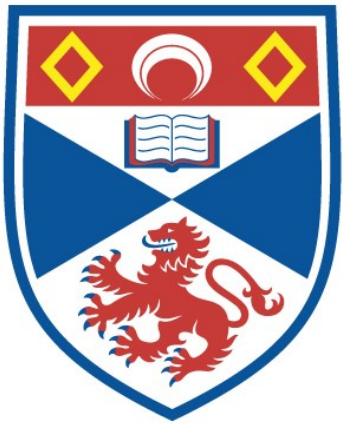
SOME ADDITION REACTIONS OF THIAZOLES

Frederick Stevens Skelton

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1965

SOME ADDITION REACTIONS OF THIAZOLES

being a Thesis

presented by

FREDERICK STEVENS SKELTON, B.A.,

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

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TO MY PARENTS

CONTENTS

DECLARATION

I declare that this thesis is based on the results of experimental work carried out by me; that it is my own composition and has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the United College in the University of St. Andrews, under the supervision of Dr. D. H. Reid.

CERTIFICATE

I hereby certify that Mr. Frederick S. Skelton, B.A., has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying thesis in application for the degree of Ph.D.

Director of Research

UNIVERSITY CAREER

I entered the University of Vermont, Burlington, Vermont, in September 1952 and graduated B.A. in Zoology and Chemistry in June, 1956. I entered Clark University, Worcester, Massachusetts in September 1957 as a postgraduate student in Chemistry, while employed at the "Worcester Foundation for Experimental Biology", Shrewsbury, Massachusetts.

The research described in this Thesis was carried out between October 1962 and June 1965.

PUBLICATIONS

1) The Addition of Dimethyl Acetylenedicarboxylate to Thiazoles: An N.M.R. Study of the Structure of the Adducts.

D.H.Reid, F.S.Skelton and W.Bonthrone, Tetrahedron Letters, 1964, 27, 1797.

2) Studies of Heterocyclic Compounds. Part I. A Synthesis of 6-Substituted Pyrrolo[2,1-b]thiazoles

B.B.Molloy, D.H.Reid, and (in part) F.S. Skelton, J.Chem.Soc., 1965, 65

ACKNOWLEDGEMENTS

I wish, especially, to thank Dr. D. H. Reid for suggesting the topic of research and for his continual interest, encouragement and advice during the course of this work.

I am also grateful to all members of the Technical Staff in the St. Andrews University Chemistry Department for assistance during the course of the experimental work and to Mrs. Reid and Miss Milly Smith, of the Secretarial Staff, for their help in the preparation of this Thesis.

My thanks are also extended to the University Grants Committee for the award of a Research Fellowship.

Summary

Possible synthetic approaches to the pyrrolo[2,1-b]thiazole system have been investigated involving the mode of addition of thiazoles to dimethyl acetylenedicarboxylate.

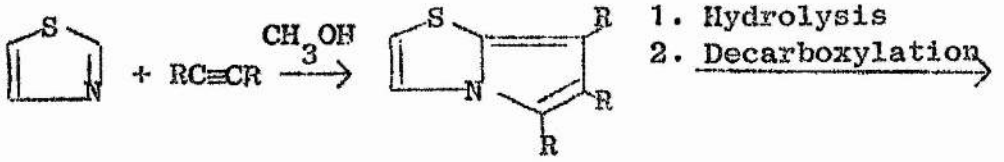
A number of thiazoles were allowed to react with the ester and the reactions were found to be remarkably solvent dependent. Dimethylformamide and methanol (or acetonitrile) were found to be specific for the formation of a particular class of adduct.

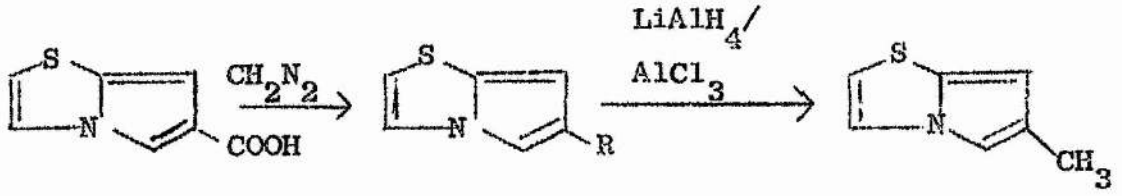
The structures of the various adducts were extensively investigated by proton magnetic resonance spectroscopy. It was found that the proton magnetic resonance spectra of the unsubstituted and monosubstituted thiazole adducts, prepared in dimethylformamide, were different from the resonance spectra of the 2,4-disubstituted thiazole adducts. Various compounds were prepared for use as proton magnetic resonance reference compounds giving strong support for the structures proposed. Various degradative methods were employed in order to gain additional evidence for the proposed structures.

Trimethyl pyrrolo[2,1-b]thiazole-5,6,7-tricarboxylate was isolated in low yield from thiazole and dimethyl acetylenedicarboxylate in methanol. Various attempts to decarboxylate the 6-carboxylic acid and isolate the parent pyrrolo[2,1-b]thiazole in good yield were unsuccessful. The 6-carboxylic acid methyl ester was reduced to 6-methyl-pyrrolo[2,1-b]thiazole with the lithium aluminium hydride/aluminium

chloride complex.

(R = CO_2CH_3)





2-Methylthiazoline formed isolable adducts with dimethyl acetylenedicarboxylate but the proton magnetic resonance spectra showed that they possessed a different structure from the corresponding 2-methylthiazole adducts.

Thiazoles did not react with ditetrahydropyranyl acetylenedicarboxylate nor with a saturated solution of acetylene in N-methyl-2-pyrrolidone.

The addition reactions of thiazoles were extended to methyl propiolate which was found to be less reactive than dimethyl acetylenedicarboxylate. Adducts could only be isolated in low yield from thiazole, 2,4-dimethylthiazole and 2-methylthiazole. The structures proposed for these adducts did not bear analogy to those isolated from dimethyl acetylenedicarboxylate.

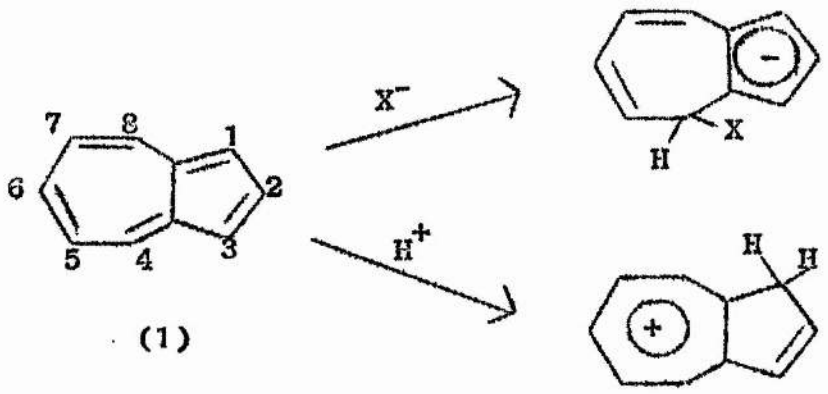
Further investigations into the preparation of pyrrolo[2,1-b] thiazoles were attempted using other methods. Low yields of

6-substituted pyrrolo[2,1-b]thiazoles were obtained from the cyclisation of acetonyl and phenacyl-2-alkylthiazolium salts in aprotic solvents. Attempted cyclisations of 3-acetonyl-2-methylthiazolium perchlorate with thionyl chloride and 3-formylmethyl-2-methylthiazolium chloride with sodium acetate and acetic anhydride gave only traces of the corresponding pyrrolo[2,1-b]thiazoles.

SECTION A

I. Introduction

Azulene (1) is an interesting molecule since its reactions with nucleophilic and electrophilic reagents demonstrate the ease with which the π-electron system of the molecule can rearrange to stabilize the intermediate anion or cation. It has been shown that electrophilic substitution occurs preferentially at C-1 and then

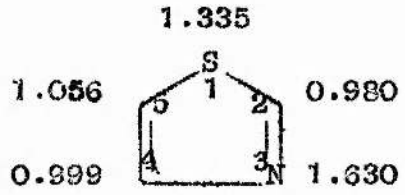


at C-3; nucleophilic substitution at C-4 or C-8.[1,2]

This led to a desire to study the substitution reactions of the heterocyclic compounds indolizine and pyrrolo[2,1-b]thiazole. Fraser [3] compared some electrophilic substitution reactions of indolizine to those of azulene and Molloy [4] studied the iso-π-electronic system pyrrolo[2,1-b]thiazole, in which the 7,8 double bond of the 6-membered ring of indolizine is replaced by the heteroatom sulphur.

Thiazoles are one of the starting materials for the synthesis of pyrrolo[2,1-b]thiazoles, analogous to the formation

of indolizines from pyridines. Thiazoles are similar to the pyridines in both physical and chemical properties. The charge distribution of thiazole (2) [5] indicates that substitution by nucleophilic reagents should occur at position C-2 and then at C-4. This has been demonstrated by amination at the C-2 position.[6]



(2)

Substitution by electrophilic reagents is difficult but should occur at position C-5. This is shown by the ready sulphonation of thiazole at position C-5,[7] especially if electron feeding groups are present at position C-2. Substituents at the C-2 position of thiazoles are very reactive as are the corresponding C-2 or C-4 positions of pyridine. The synthesis by Hantzsch [8] is the most useful means of preparing thiazoles.

II. Preparation of pyrrolo[2,1-b]thiazoles

[A] The Application of indolizine syntheses

A number of syntheses of substituted and unsubstituted indolizines are described in the literature which could be applied to the synthesis of pyrrolo[2,1-b]thiazoles. It was especially desirable to find a suitable synthesis of pyrrolo[2,1-b]thiazole itself for substitution studies.

(1) Scholtz Synthesis

The reaction of 2-methylthiazole with acetic anhydride to give the corresponding acetyl pyrrolo[2,1-b] thiazoles, analogous to the formation of indolizines from 2-picoline, has been attempted.[9] Only traces of product were formed probably due to deactivation of the nucleophilic nitrogen atom by the inductive effect of the sulphur atom.

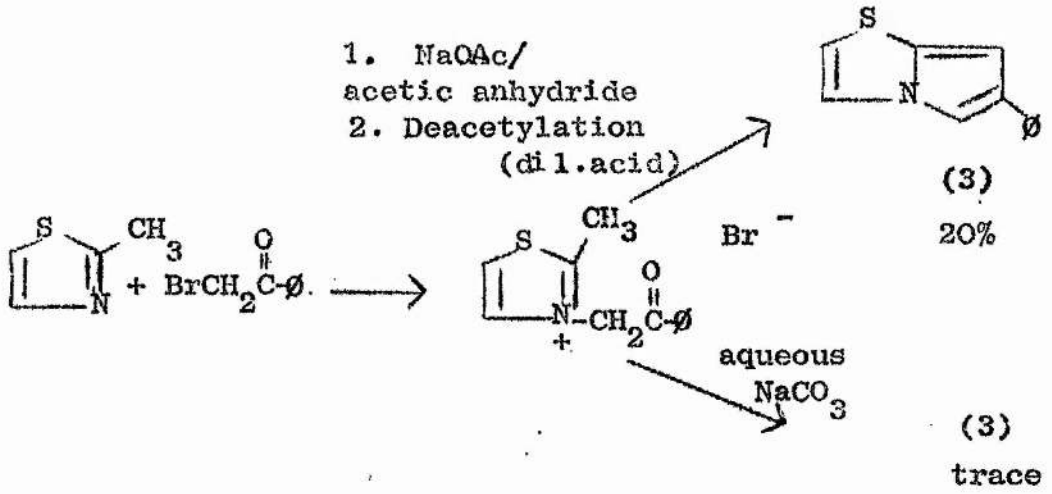
(2) Chichibabin Synthesis

The reaction of alkyl thiazoles with α-halo carbonyl compounds and subsequent cyclisation of the quaternary salt has been realised.[4,10] This is analogous to the formation of indolizines from alkyl pyridines.

Quaternary salts were usually isolated as the bromide or perchlorate. No crystalline quaternary salts could be prepared from bromodiacetyl and ethyl bromopyruvate, desirable as precursors to unsubstituted pyrrolo[2,1-b] thiazoles, and they were subjected to cyclisation conditions directly according to the method of Borrows and Holland.[9]

Cyclisation of 2,4-dimethyl-3-phenacylthiazolium bromide with aqueous sodium carbonate gave a low yield of 3-methyl-6-phenylpyrrolo[2,1-b] thiazole.[11] Cyclisation of 2-methyl-3-phenacylthiazolium bromide with aqueous sodium carbonate gave traces of 6-phenylpyrrolo[2,1-b] thiazole (3),[4] but boiling under reflux with sodium acetate in acetic anhydride and subsequent deacetylation by acid hydrolysis gave the 6-phenylpyrrolo[2,1-b]

thiazole (3) in 20% yield.[12] This latter method was found to be general for the preparation of 6-substituted pyrrolo[2,1-b] thiazoles, but the preparation of the parent base, and pyrrolo[2,1-b] thiazoles



unsubstituted in the pyrrole ring still had to be realised.

[B] Other Methods

(1) Attempted reduction and cyclisation of ethyl-2-benzothiazolylpyruvate

The attempted preparation of pyrrolo[2,1-b] thiazoles by reduction of ethyl-2-benzothiazolylpyruvate with sodium borohydride, treatment with hydrobromic acid and cyclisation with alkali failed at the reduction stage.[4]

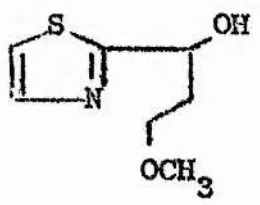
(2) Attempted cyclisation of 1,2-vinyl, 1,3-methoxy, and 1,3-chlorocarbinols

The 1,2-vinylcarbinol (4) was prepared from the reaction of 2-thiazolyl lithium with α,β unsaturated aldehydes or ketones.

The 1,3-methoxycarbinol (5) was prepared from 2-thiazolyl lithium and 3-methoxypropionaldehyde, and 1,3-chlorocarbinol (6) was prepared from 2-thiazolyl lithium and 3-chloropropionaldehyde.

The vinylcarbinol (4) was treated with dilute acid followed

(4)



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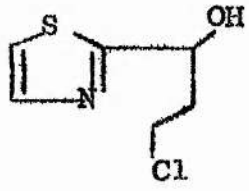
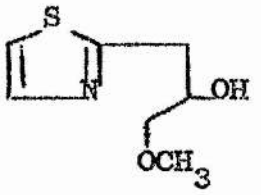


(6)

by alkali and the carbinols (5) and (6) were treated with concentrated hydrobromic acid followed by alkali. In each case only traces of pyrrolo[2,1-b]thiazole were detected by Ehrlich's reagent.[4]

(3) Attempted cyclisation of 2,3-methoxy and 2,3-chlorocarbinols

The 2,3-methoxycarbinol (7) was prepared from 2-thiazolyl lithium and 3-methoxyepoxypropane, and 2,3-chlorocarbinol (8) was prepared from 2-thiazolyl lithium and epichlorohydrin.



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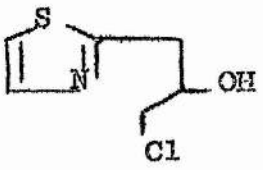
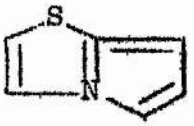


(8)

Cyclisation of the carbinol (7) with hydrobromic acid followed by alkali gave traces of pyrrolo[2,1-b] thiazole.

Cyclisation of the carbinol (8) by boiling under reflux with t-butanol gave pyrrolo[2,1-b] thiazole (9) in 1.9% yield.[4]

(8) —boiling t-butanol→ 

(9)

1.9%

(4) Attempted synthesis involving closure to a thiazole ring

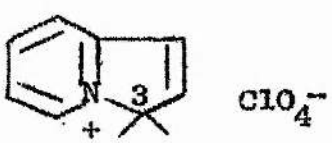
The closure to a thiazole ring was not realised due to inaccessibility of the required 2-mercaptopyrrole.[4]

III. Some substitution reactions of 6-substituted pyrrolo[2,1-b] thiazoles compared with Indolizine

6-Substituted pyrrolo[2,1-b] thiazoles could be acetylated,[13,14] formylated [15,16,17] and nitrosated[18] at the C-5 position analogous

to the corresponding reactions of indolizine, but were more unstable to the conditions employed in the indolizine series.

The nuclear magnetic resonance spectra of indolizinium perchlorate (10) [19] and pyrrolo[2,1-b]thiazolium perchlorate (11) [20] in trifluoroacetic acid, show that protonation takes place at C-3 in the perchlorate (10) and at C-5 in the corresponding perchlorate (11).



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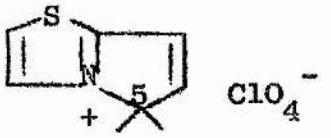


(11)

The results of substitution reactions on pyrrolo[2,1-b]thiazoles show that they have a lower degree of polarisation in the ground state than do the corresponding indolizines. It would be desirable to study the substitution reactions of the parent base and compare the results with molecular orbital calculations for frontier electron densities and localisation energies, when these become available.

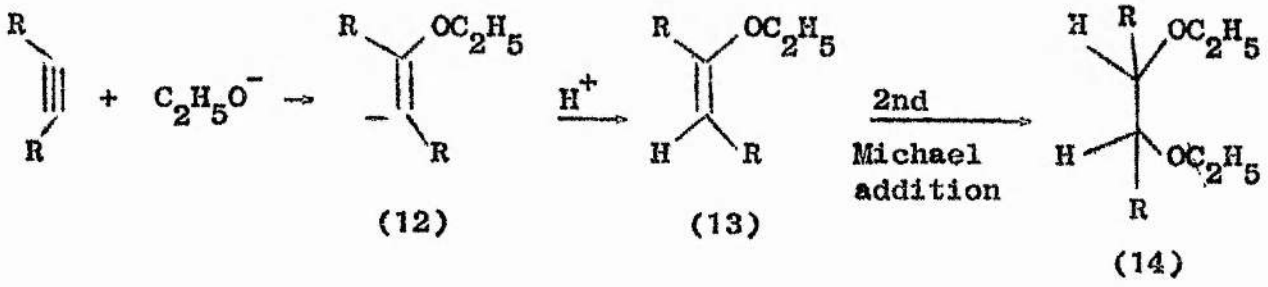
Since pyrrolo[2,1-b]thiazole has only been prepared in low yield, it seemed desirable to study the addition of thiazoles to dimethyl acetylenedicarboxylate, analogous to known additions of other heterocyclic compounds, as a possible route to

pyrrolo[2.1-b] thiazoles. During the course of this work, several interesting classes of adduct were obtained and the majority of this thesis is concerned with the determination of their structures.

The following section includes a short summary of the addition reactions of pyridines to dimethyl acetylenedicarboxylate in a variety of solvents. A number of structures will be discussed in detail since they are similar to some proposed structures described in this thesis.

IV. The addition of heterocyclic compounds to acetylenic esters

Acetylenic esters are known to undergo Michael type addition reactions with alkoxide ion. An example is the formation of diethyl ethoxy-fumarate (13) and maleate and some diethyl diethoxysuccinate (14) from the reaction of diethyl acetylenedicarboxylate with ethoxide ion.[21]



(R = $CO_2C_2H_5$)

The addition reactions of heterocyclic compounds are analogs of the above reaction and can be considered to involve the formation of an intermediate anion of the type (12).

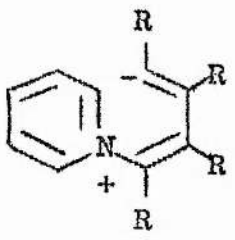
A number of addition reactions of heterocyclic compounds (i.e Acridine,[22] phenanthridine,[23,24] 2,3-benzacridine,[25] pyrrole[26,27,28] and 2-methylpyrrole,[29] indole,[30] 4-methylimidazole,[27,29] quinoline[31] and isoquinoline[32]) have been described.

[A] Pyridine

(1) The addition of pyridine and 3-methylpyridine to dimethyl acetylenedicarboxylate in ether at room temperature

Diels and co-workers,[26,33,34] isolated three quinolizine derivatives from pyridine and dimethyl acetylenedicarboxylate in ether, a red "labile" adduct (15), a yellow "stable" adduct (16) and Kashimoto's adduct (17).

(R = CO_2Me in all formulae)



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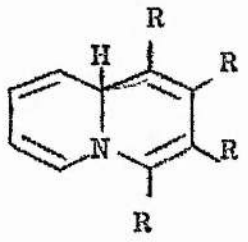

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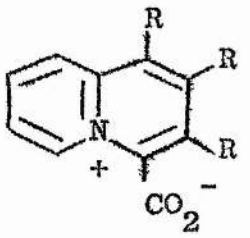


(17)

A number of papers describing analogous structures from other heterocyclic compounds (i.e. quinoline,[26,33,35] isoquinoline,[35] acridine,[36] and phenanthridine[37]) have appeared.

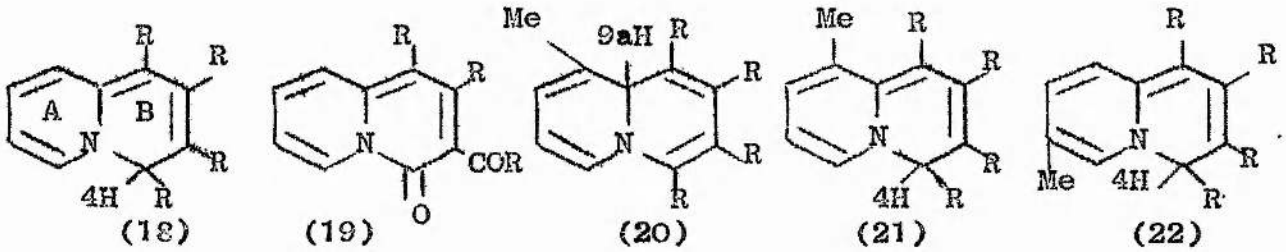
Acheson and co-workers[22,23,31,32] have reinvestigated this work using modern analytical methods and found that many of the structures proposed by Diels had to be revised.

Acheson and Taylor[38] added pyridine to dimethyl acetylene-dicarboxylate in ether at room temperature and obtained yellow

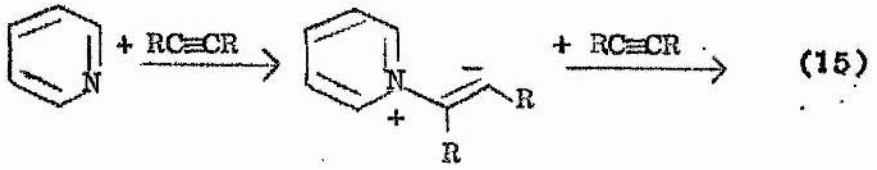
plates of Diels' and Alder's 9aH-quinolizine adduct (16). It is now believed to have the 4H-quinolizine structure (18).[38] A small amount of a product called Kashimoto's compound is believed to have the structure (19).[39]

The addition of 3-methylpyridine to dimethyl acetylenedicarboxylate in ether at room temperature gave the orange 9aH-quinolizine adduct(20) and a yellow 4H-quinolizine adduct (21). A yellow brown 4H-quinolizine adduct (22) was isolated from a reaction carried out in hot benzene.[38]

(Me = CH_3 in all formulae)



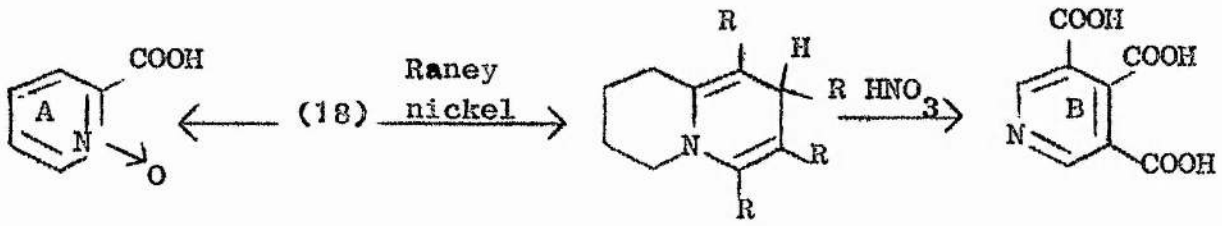
The suggested mechanism for formation of the 4H-quinolizine (18) from pyridine involves the isomerisation of the 9aH-quinolizine (16), which Diels thought was the zwitterion (15).[33] This structure is probably formed by the stepwise addition of two molecules of dimethyl acetylenedicarboxylate, as shown, but has not been rigorously proved.



cyclisation → (16) isomerisation → (18)

(a) Chemical evidence for the structures of 4H and 9aH-quinolizines

Diels and Alder [34] showed the presence of ring A by oxidation of the 4H-quinolizine (18) to pyridine-2-carboxylic acid N-oxide (23) and Acheson and Taylor [38] showed the presence of ring B by nitric acid oxidation of the tetrahydro derivative (24), obtained from Raney nickel hydrogenation of the 4H-quinolizine (18),



(23) (24) (25)

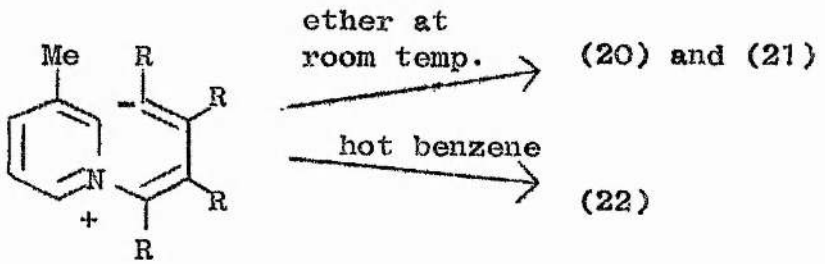
to the pyridine-3,4,5-tricarboxylic acid (25). The pyridine-3,4,5-tricarboxylic acid was further decarboxylated over soda-lime to pyridine. Complete hydrogenation of the 4H-quinolizine (18) over Raney nickel gave tetramethyl perhydroquinolizine-1,2,3,4-tetracarbcxylate, confirming the bicyclic structure. This was independently proven by Woodward [39] from quantitative hydrogenation experiments.

In a similar manner the structure of the 9aH-quinolizine (20) has been proved by Raney nickel hydrogenation and oxidation to pyridine-3,4,5-tricarboxylic acid (25).[38] It was proved that Raney nickel did not cause isomerisation to the stable adduct.

The 9aH-quinolizine (20) could be converted to the more stable 4H-quinolizine (18) by boiling under reflux in benzene.

The 9aH-proton may be sterically immobilised by the C-9 methyl group preventing ready isomerisation to the 4H-quinolizine (18). This ready isomerisation may be the reason why no unsubstituted 9aH-quinolizine can be isolated from the pyridine reaction. Recent molecular orbital calculations indicate that the order of stability should be 4H (18) > 2H > 9aH (20) [40] which agrees with experimental findings. It is interesting that no 2H-quinolizines are known at the present time.

The products from 3-methylpyridine can now be rationalised in terms of slow isomerisation of the 9aH-quinolizine (20) to the 4H-quinolizine (21), responsible for the presence of both products in the reaction mixture. Evidently attack by the zwitterion (26) occurs at the α-carbon atom adjacent to the C-3 methyl group under these conditions. However, in hot benzene, attack by the zwitterion occurs at the other α-carbon atom and the 9aH-quinolizine formed immediately isomerises to the stable 4H-quinolizine (22), the only observed product.



(26)

(b) Spectral evidence for the structure of 4H and 9aH-quinolizines

(i) Ultraviolet spectra

The ultraviolet spectra [38] for the 9aH-quinolizines

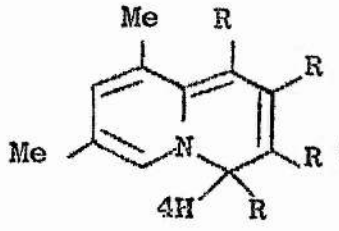
and the 4H-quinolizines were consistently similar within a series (See Table I) and consistent with the isomerisation of 9aH-quinolizines to the more conjugated 4H-quinolizines.

The ultraviolet spectra of the perchlorates of the 4H-quinolizines suggest protonation at the C-3 position except in 9-substituted adducts where steric strain forces C-1 protonation (tetrahedral carbon relieves this strain). If the 4H-quinolizines were open chain structures, it would be difficult to explain the absence of N-protonation and the steric effect. N-protonation would effect a bathochromic shift as in the protonation of quinoline.[41] The shifts here are hypsochromic (See Table I).[42] Recent proton magnetic resonance determinations of the 4H-quinolizines in trifluoroacetic acid have confirmed the results of the ultraviolet spectra of the perchlorates (See Table II).

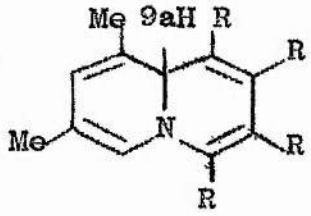
(ii) Proton magnetic resonance

Proton magnetic resonance studies [38] (See Table II) showed that the methyl protons of the 4H-quinolizine (27) are deshielded relative to those in the 9aH-quinolizine (28) suggesting that ring A in the 4H-quinolizine could sustain a larger ring current, but no model compounds were employed for comparison. Independent study by Jackman, Johnson and Tebby [43] led them to suggest the 4H-quinolizine structure on the basis of chemical evidence since proton magnetic resonance could not distinguish between a cyclic and an open chain structure. It was also

shown that the dihydropyridine (29) possessed little ring current compared to the model compound (30) so that the 4H-quinolizine cannot have a structure analogous to the structure (29). However, Acheson claims that the 4H-quinolizines are vinylogous



(27)



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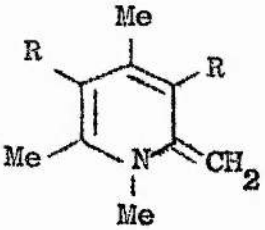

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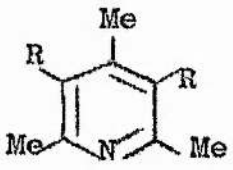


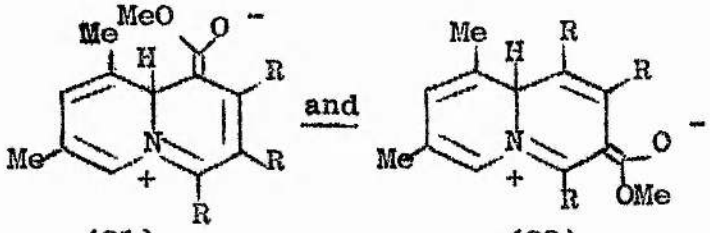
(30)

pyridones and would be expected to possess a ring current in the aromatic region.[42] Proton magnetic resonance has shown that the quinolizines do possess a greater ring current than 1-methylpyridone[44] and the 1-ester group was found to abnormally deshield the 9-proton of the 4H-quinolizine (22). Recent discussion of the validity of determining the aromaticity of a system by measuring ring current has appeared in the literature.[45,46] In summary, one must be careful in drawing conclusions about aromaticity from apparent ring current effects until more exact model compounds are available.

The absence of a methylene doublet and the existence of coupling(J = 2 c/sec.) with the C_6 and C_8 protons confirms position 9a for the single proton of the 9aH-quinolizine (20).

The ester methyl protons were carefully considered in terms of charged zwitterionic structures such as (31) and (32).[38] It was concluded that the 9aH-quinolizine (28) was the correct structure since the spectrum showed an upfield group of six ester protons

and another group of six ester protons at slightly lower field. This indicates that charge can be transferred to C-1 and C-3 carbomethoxy groups and therefore no C-2 or C-4 protons are present. The 4H-quinolizine (27) showed evidence for a C-4 proton

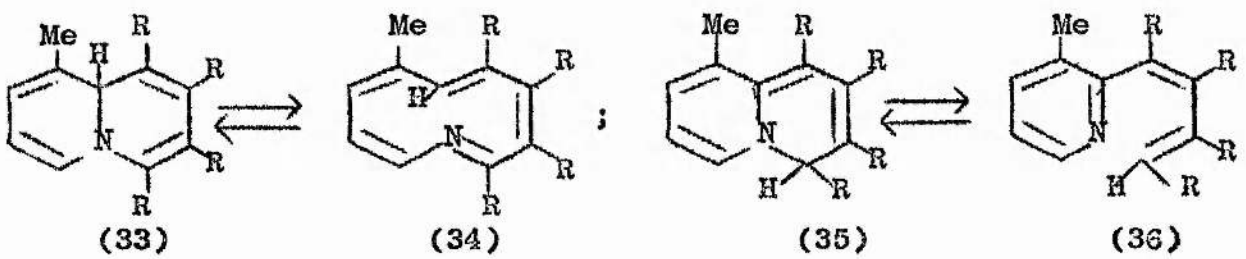


(31) and (32)

since the chemical shift, δ 6.08 is indicative of a proton adjacent to nitrogen.[38] (See Table II).

The proton magnetic resonance spectrum of the quinoline adducts [47] showed that similar structures could be considered for the adducts, but the low field proton of the analogous 4H-adduct was thought to be of the maleic or fumaric ester type since it was observed to be 1 part per million to lower field than in the corresponding pyridine adduct. Acheson,[31] however, attributes this added shift to ring current effects from the added ring.

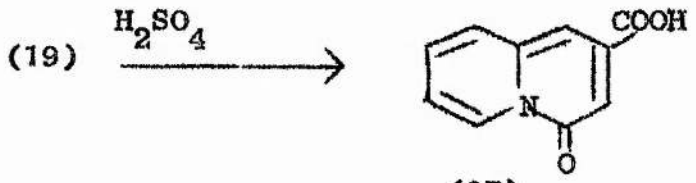
A proposal by Jackman, Johnson and Tebby [43] that the quinolizine adducts, in both the pyridine and quinoline series, may exist as the valence tautomers (33-34) and (35-36) cannot be ruled out. (Example, quinolizine adducts from 3-methylpyridine).



(33) (34) (35) (36)

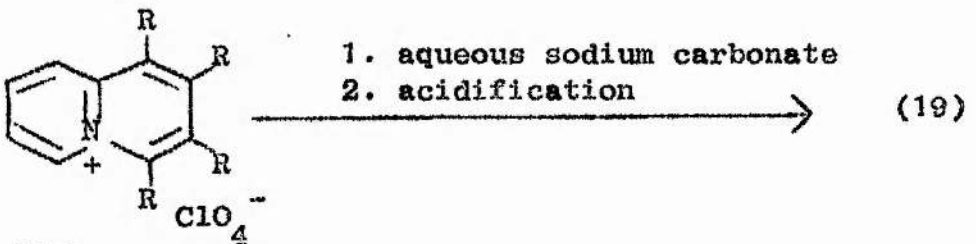
(c) The structure of Kashimoto's compound

Recent work has clarified the structure of Kashimoto's compound isolated by Diels from pyridine and dimethyl acetylenedicarboxylate in ether. Woodward [39] proposed the structure (19) since treatment with concentrated sulphuric acid formed quinolizin-4-one-2-carboxylic acid (37).



(37)

Kashimoto's compound has recently been formed from 1,2,3,4-tetramethoxycarbonylquinolizinium perchlorate (38) by treatment with aqueous sodium carbonate and subsequent acidification.[48] A similar mechanism may govern its formation along with the 9aH and 4H- quinolizines, from the reaction of pyridine with dimethyl acetylenedicarboxylate.

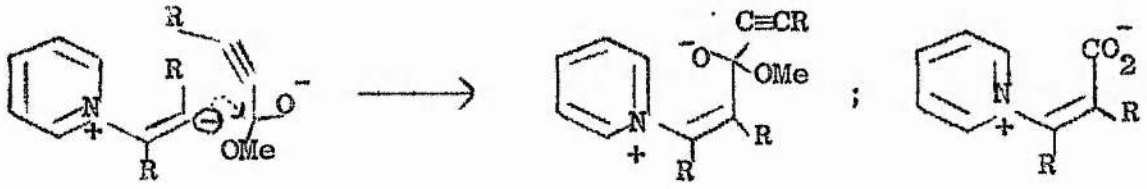


(38)

(2) The addition of pyridine and 3-methylpyridine to dimethyl acetylenedicarboxylate in ether at low temperature.

Pyridine and 3-methylpyridine form cream coloured (1:2) adducts with dimethyl acetylenedicarboxylate in ether at -50°,[43]

which are unstable and give off carbon dioxide at room temperature. It was suggested that the ylid (26) was a possible structure but unlikely since yields of the quinolizines (20), and (21) were small. However, the infrared spectrum showed strong acetylenic type vibrations in the region 2100-2200 cm^{-1} and the structure (40) was suggested.[49] This presumably arises from attack of the initial zwitterion (39) on the ester carbonyl of a second molecule of the acetylenic ester. Support for the initial zwitterion (39) comes from



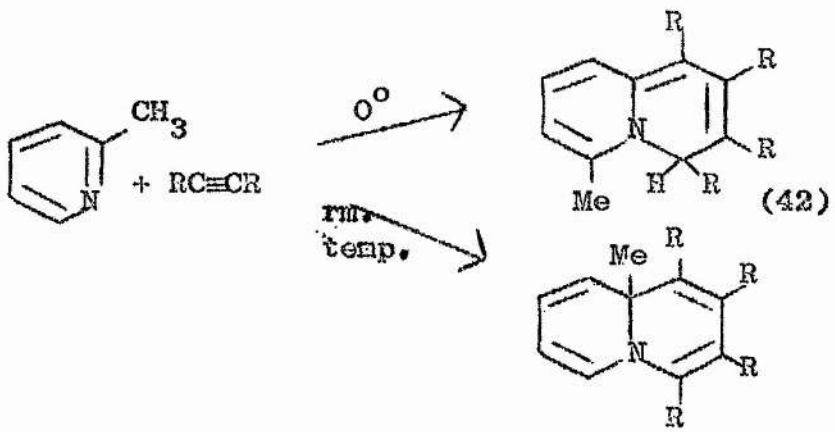
(39) (40) (41)

the isolation of the adduct (41) from pyridine, dimethyl acetylenedicarboxylate and carbon dioxide at -60°.[50]

(3) The addition of α-picoline to dimethyl acetylenedicarboxylate at 0°.

Diels and Pistor [51] were able to isolate the 4H-quinolizine (42) from the reaction of α-picoline and dimethyl acetylenedicarboxylate at 0° and the 9aH-quinolizine (43) from the same reaction at room temperature. Acheson [52] was only able to isolate the adduct (43). Since his reaction conditions were not explicit, it seems that he was working at or close to room temperature. It appears that cyclisation at 0° occurs at the unsubstituted α-carbon atom

and the 9aH-quinolizine formed further isomerises to the 4H-quinolizine (42).



(43)

(4) The formation of indolizines

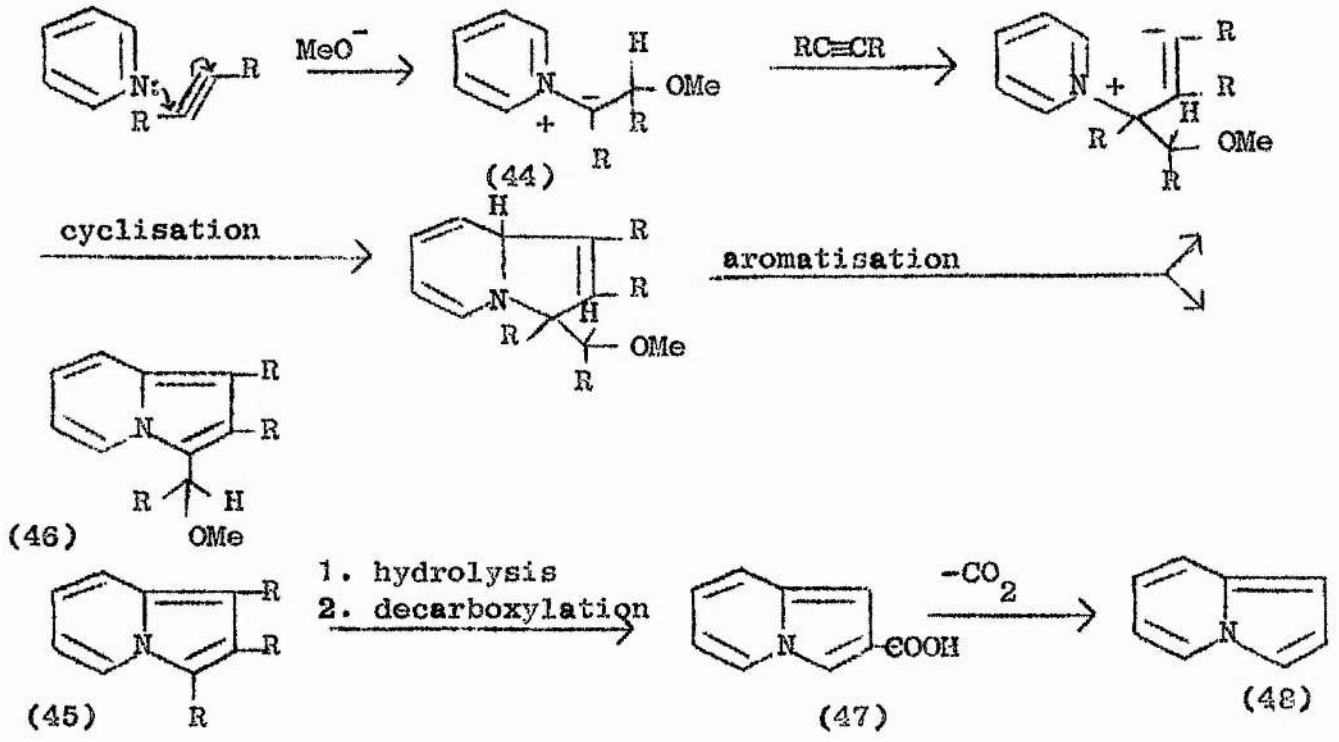
This is the most interesting reaction of the series since the object of the work described in this thesis was to find a more satisfactory route to pyrrolo[2,1-b]thiazole. The analogous reaction in the thiazole series would give us the required pyrrolo[2,1-b]thiazole system.

Early work [34] showed that the 4H-quinolizines could be converted to trimethyl indolizine-1,2,3-tricarboxylate (45) by (a) treatment with bromine followed by hydrolysis or (b) oxidation with nitric acid.

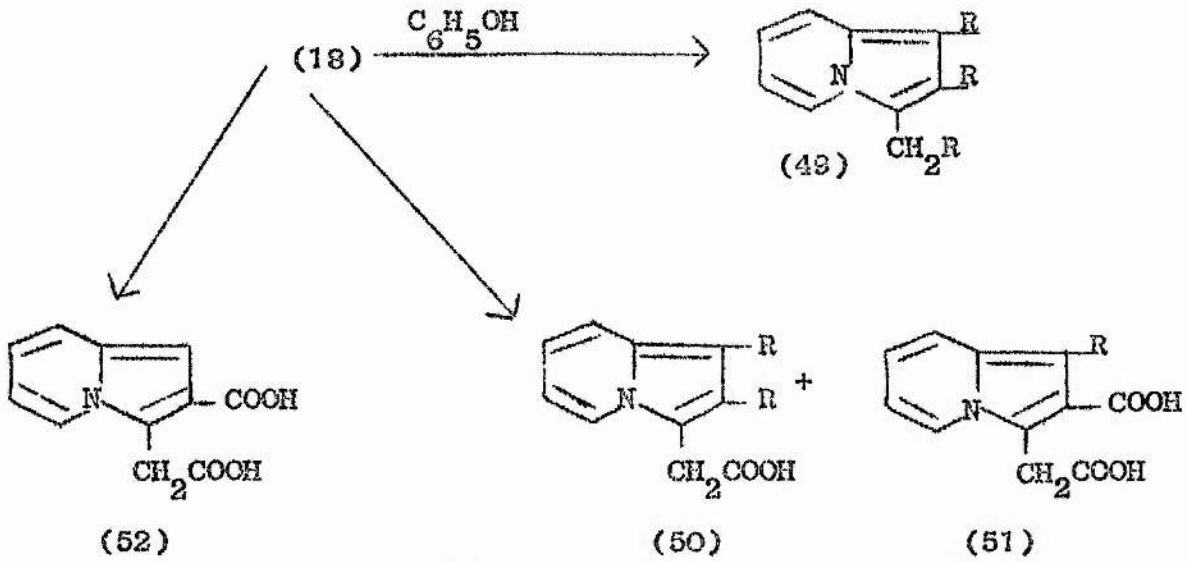
Wiley and Knabeschuh [56] obtained the triester (45) from the reaction of pyridine and dimethyl acetylenedicarboxylate in ether at -78° and allowing the mixture to stand at -20° for 20 hours. Highest yields (20%) were obtained only if traces of water, methanol or peroxides were present. Hydrolysis

of the triester with potassium hydroxide and decarboxylation of the precipitated acid, on warming with dilute hydrochloric acid, gave the 2-carboxylic acid (47) whose ultraviolet spectrum was the same as that of an authentic sample. The calcium salt of the 2-carboxylic acid (47) on decarboxylation gave indolizine (48).[34]

The addition of pyridine to dimethyl acetylenedicarboxylate in methanol at room temperature gave a mixture of two indolizines.[54,55] Acheson and Plunkett [23] have proposed the following mechanism for their formation. Nucleophilic attack of pyridine on the ester is followed by addition of methoxide ion forming the zwitterion (44). Addition of another molecule of ester, cyclisation and subsequent aromatisation would give the indolizines (45) and (46).

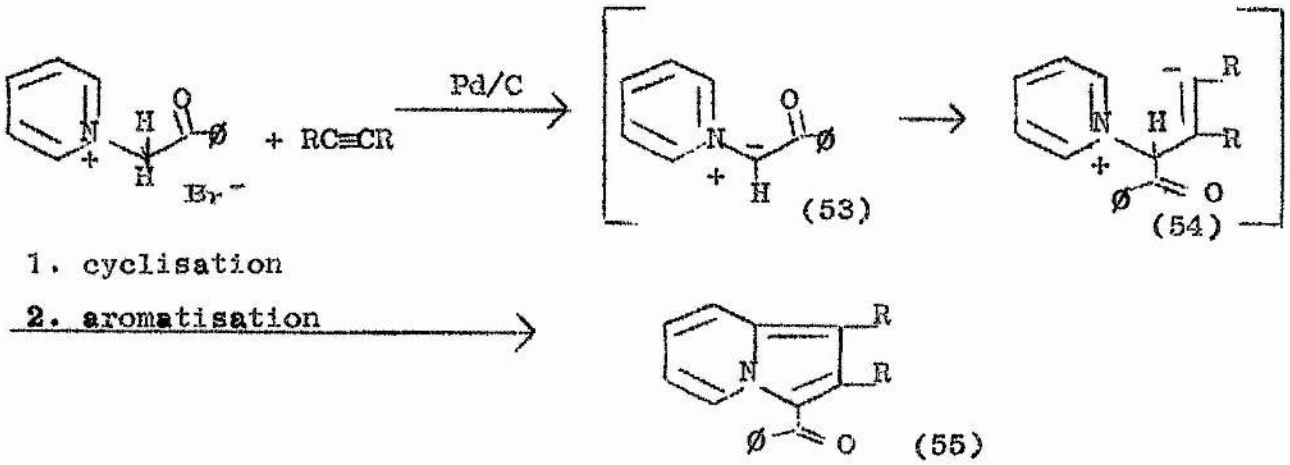


The 4H-quinolizine (18) was shown to give derivatives of indolizine-3-acetic acid on treatment with phenol, formic acid or potassium hydroxide.[53] Mechanisms to describe the formation



of the compounds (49)-(52) have not been given.

An interesting use of dimethyl acetylenedicarboxylate is in the formation of the indolizines (55) from the zwitterions (53) and (54) derived from 1-phenacyl pyridinium bromide in the presence of palladium-on-charcoal.[57] The indolizine (55) was smoothly converted into indolizine-2-carboxylic acid (47)

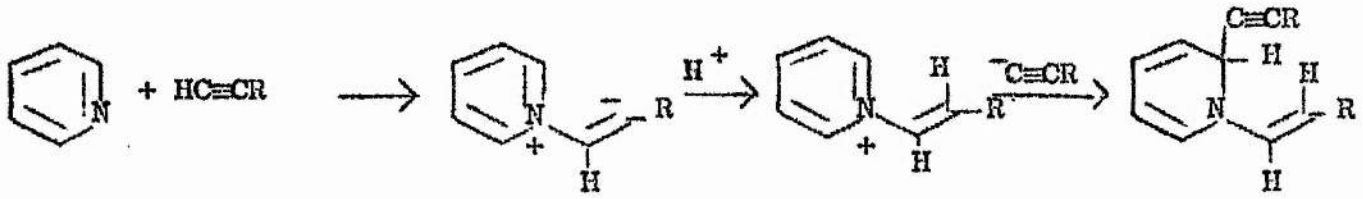


on hydrolysis and subsequent treatment with mineral acid. The acid (47) was identical to an authentic sample prepared by the Chichibabin reaction of 2-picoline and ethyl bromopyruvate.

(5) The addition of pyridine and 2-aminopyridine to methyl propiolate.

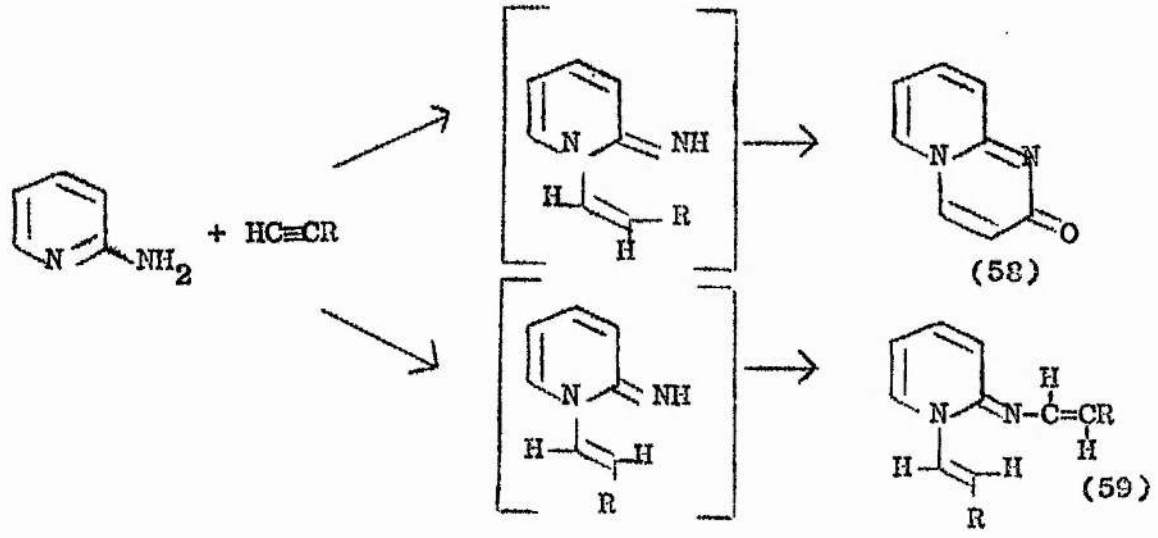
Addition reactions of heterocyclic compounds to methyl propiolate have not been extensively investigated.

The product from pyridine is an unstable adduct which is considered to be the 1,2-dihydropyridine (57). This is regarded as resulting from the attack of an acetylide anion on the α-carbon atom of the pyridinium cation (56).[55]



(56) (57)

2-Aminopyridine and methyl propiolate in ether gave a mixture of of 2H-pyrido[1,2-a]pyrimidine-2-one (58) and compound (59).



(58) (59)

SECTION B

DISCUSSION

I. The Addition of Thiazoles to Dimethyl Acetylenedicarboxylate

Diels and Meyer [54] described the formation of trimethyl indolizine-1,2,3-tricarboxylate from the reaction of pyridine with dimethyl acetylene dicarboxylate in methanol. Since then a number of investigators notably Acheson,[22,23,31,32] Woodward [39] and Johnson [43,55] have re-investigated the work of Diels on the addition of various nitrogen-containing heterocyclic compounds to dimethyl acetylenedicarboxylate and concluded that the majority of products are bicyclic (See Introduction).

Close examination of the literature failed to indicate any significance placed on "solvent effects" and no attempts were made to carry out a systematic study of the reactions in specific solvents.

It was decided to examine the reactions of thiazoles with dimethyl acetylenedicarboxylate in ether, dimethylformamide, methanol and acetonitrile. One millimole reactions of each thiazole employed were carried out at room temperature with two millimole of the ester in 2 ml. of each solvent. The reactions were allowed to proceed for 96 hours during which time the progress was followed by thin-layer chromatography using "silica gel G". Dimethylformamide and methanol (sometimes acetonitrile) were found to be specific for the formation of

particular adducts which were then isolated from reactions performed on the 20 mmole scale.

For clarity, the adducts will be designated by a numbered formula which does not always represent a proposed structure.

[A] The preparation of thiazoles and dimethyl acetylenedicarboxylate.

Thiazole was prepared by diazotisation and deamination of 2-aminothiazole.[59]

2-Methylthiazole,[60] 4-methylthiazole [61] and 2-ethylthiazole [62] were prepared by the reaction of an α-halocarbonyl compound with the corresponding amide and phosphorus pentasulphide. 2-t-Butylthiazole was prepared from the preformed thiopivalamide, prepared by the reaction of pivalamide with phosphorus pentasulphide in pyridine.[63] 2,4-Dimethylthiazole, 2,5-dimethylthiazole, 2-ethyl-4-methylthiazole and 2,4,5-trimethylthiazole were prepared by an improvement over the above method as developed by Kurkjy and Brown,[64] and gave a better yield of product than could be obtained by the literature methods. 2,4,5-Trimethylthiazole contained an impurity which was removed by careful chromatography through a long column of alumina.

All thiazoles were individually checked for purity on a Perkin Elmer 451 gas-liquid chromatograph before being used.

Dimethyl acetylenedicarboxylate was prepared by esterifying acetylenedicarboxylic acid with methanolic sulphuric acid

according to the method of Huntress, Lesslie and Bornstein.[65]

[B] The addition of thiazoles to dimethyl acetylenedicarboxylate in dimethylformamide.

The addition of 2,4-dialkyl and trialkylthiazoles to dimethyl acetylenedicarboxylate in dimethylformamide gave a class of adducts formulated as the [3,4,0]-bicyclic structures, 8a*H*-thiazolo[3,2-*a*]pyridines, which could easily be separated by chromatography from traces of accompanying yellow products. In the single case of 2-ethyl-4-methylthiazole, a low yield of a white isomer (60) was also isolated but the structure was not extensively investigated.

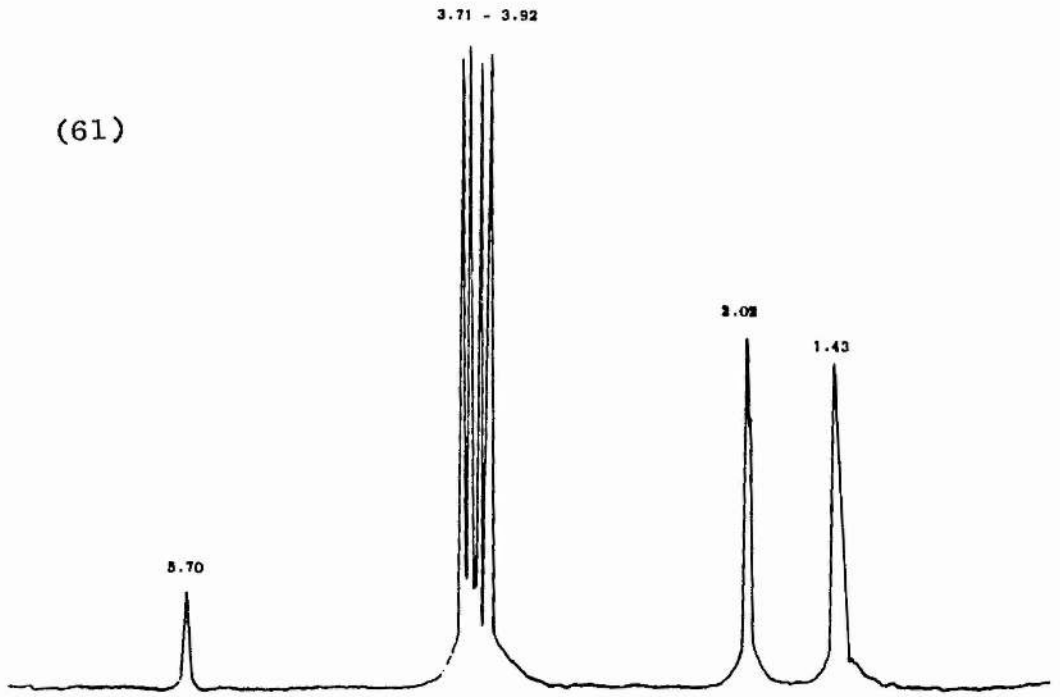
(a) Proton magnetic resonance

It was decided to make extensive use of proton magnetic resonance spectroscopy in elucidation of structure since these compounds could be studied in their ground state. Any perturbations or rearrangements which might occur when the molecule was in a higher energy state during reaction, would then be avoided.

The proton magnetic resonance spectrum (Plate 1) of the structure (61) in deuterochloroform showed a group of signals (12H) at δ 3.71 - 3.92 ($4CO_2Me$). One group ($2CO_2Me$) appeared slightly downfield from the other group ($2CO_2Me$) in agreement with the findings of Acheson [38] for the analogous 8a*H*-quinolizines (See Table II, end of thesis). A singlet (3H)

PLATE 1.

(61)



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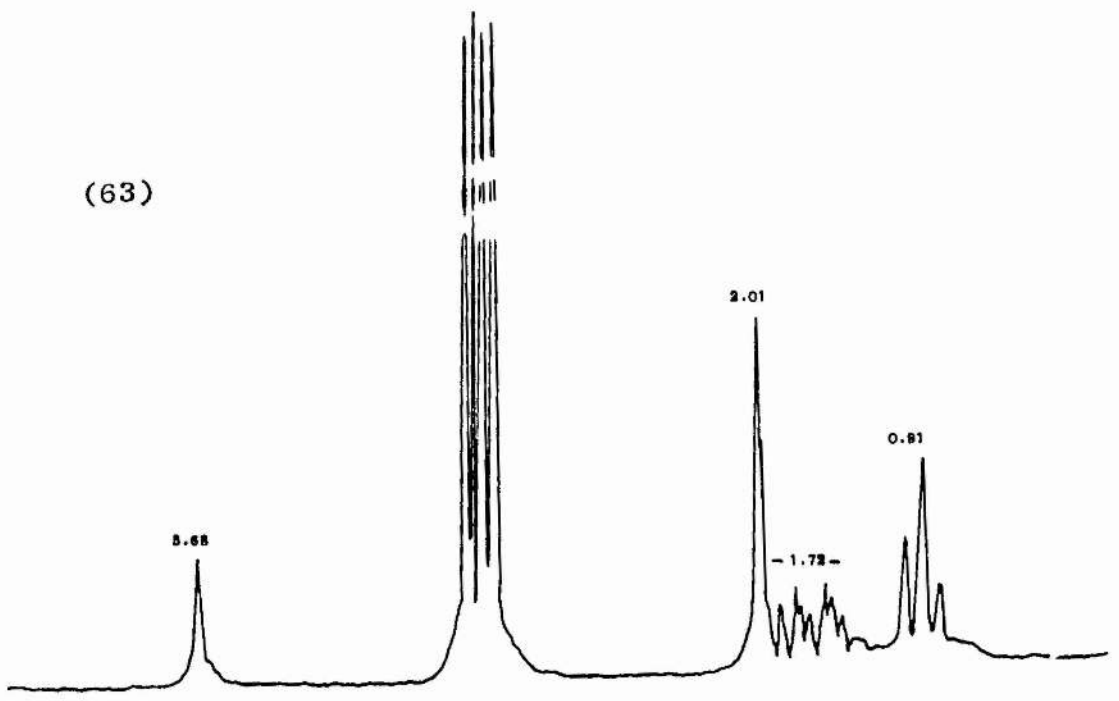
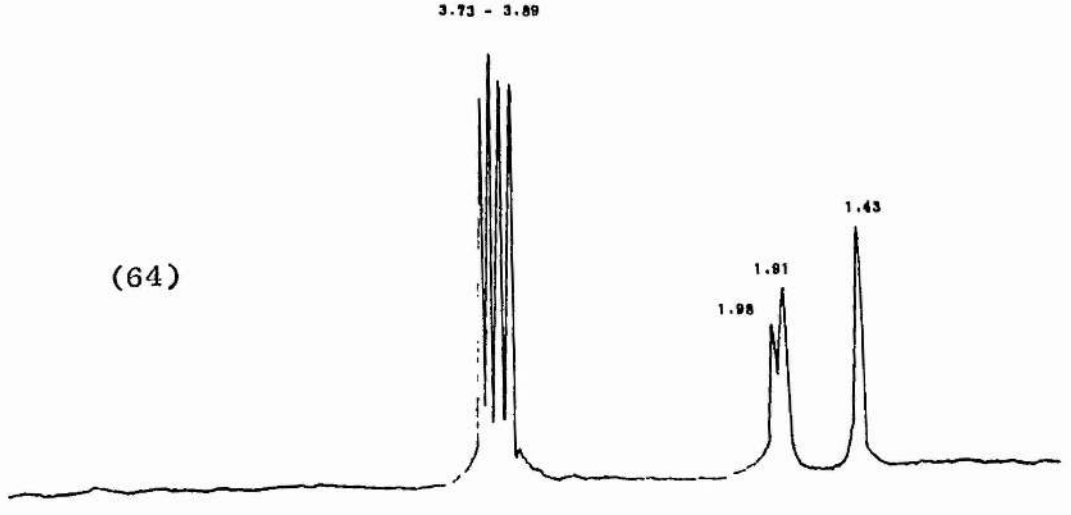
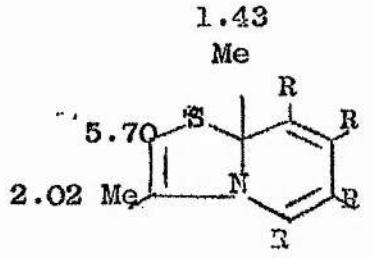


(64)



appeared at δ 1.43 (CH_3), a weakly resolved doublet (3H) at δ 2.02 (CH_3) and a broad unresolved line (1H) at δ 5.70.



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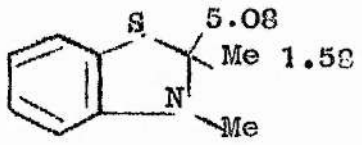
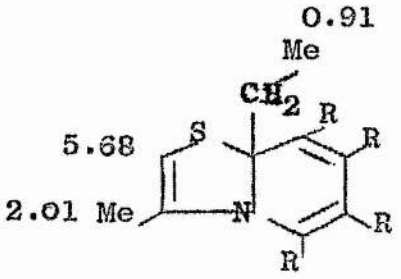


(62)

The signals at δ 2.02 arise from the protons of what was the 4-methyl group of 2,4-dimethylthiazole. There is slight allylic coupling [66] of the protons through four bonds (J = 1.1 c./sec.) to the C-2 proton (what was the C-5 proton of 2,4-dimethylthiazole). The chemical shift of the protons of the methyl group at δ 1.43 is in agreement with a value of δ 1.58 for the chemical shift of the 2-methyl protons in the model compound 2,3-dimethyl-2,3-dihydrobenzothiazole (62). This methyl group must be on a tetrahedral carbon atom. These data suggest that cyclisation has taken place at the C-2 position of 2,4-dimethylthiazole.

The proton magnetic resonance spectra of the structures (63) and (64) from 2-ethyl-4-methylthiazole and 2,4,5-trimethyl thiazole were similar and in agreement with an analogous structure. The signal arising from the methyl protons (3H) at δ 1.91 in compound (64) must be the methyl group adjacent



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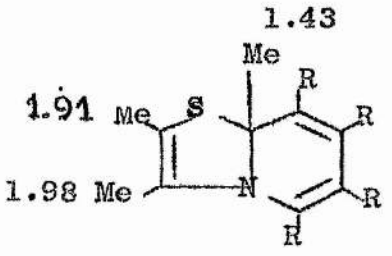


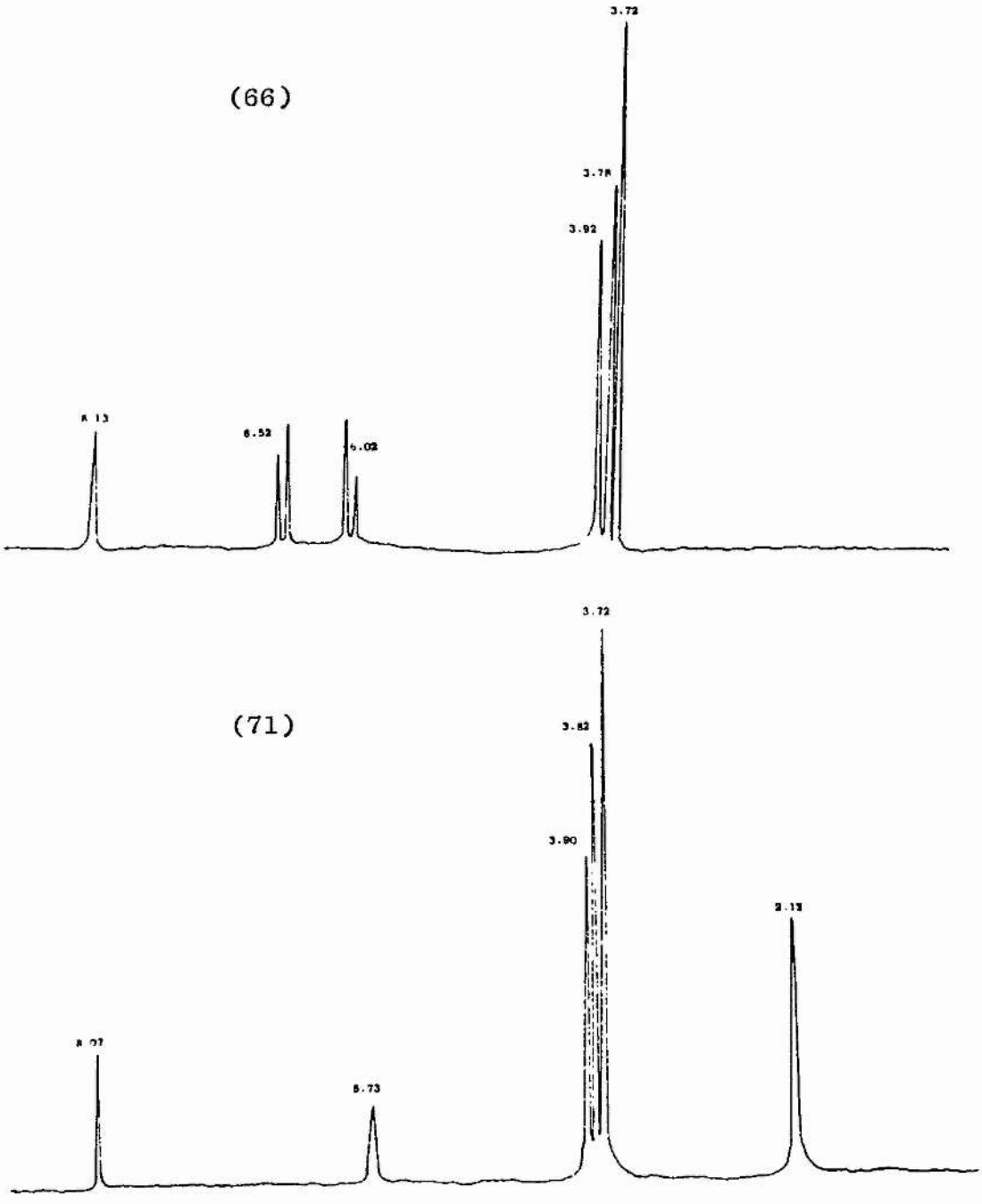
(64)

to sulfur in agreement with a slight upfield shift relative to the methyl protons at δ 1.98 adjacent to nitrogen in the same compound. In the compound (63) the signals of the methylene protons are split into a quadruplet by the adjacent methyl protons, as would be expected. The signals of the methyl protons (3H) of the ethyl group appear as a triplet centred at δ 0.91 and are further shielded by the methylene protons.

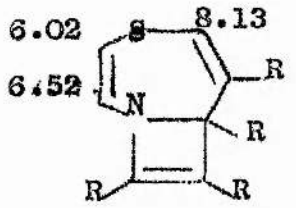
The addition of thiazole, monoalkyl and 2,5-dialkyl thiazoles to dimethyl acetylenedicarboxylate in dimethylformamide gave what we consider to be members of another class of adducts containing the [5,2,0]-bicyclic structures, 8aH-azeto[1,2-d] [1,4]thiazepines (or the nine-membered ring 1,4-thiazonines). The major product was separated from traces of polar material by chromatography and, in the case of 2-alkylthiazoles, from traces of an accompanying yellow product. 2-Ethylthiazole also gave a white isomer (65) having a similar proton magnetic resonance spectrum to that of the isomer from 2-ethyl-4-methylthiazole.

The proton magnetic resonance spectrum (Plate 2) of the structure (66) in deuterochloroform showed a group of signals (12H) at δ 3.72 - 3.92 ($4CO_2Me$), two doublets of an AB system (2H)

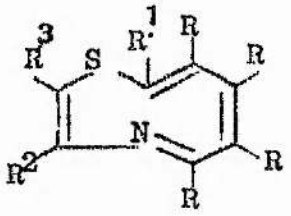
PLATE 2.



centred at δ 6.02 and 6.52 (J = 4.75 c./sec.) and a singlet (1H) at δ 8.13. The lines of the AB system arise from the two

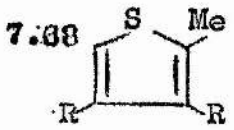


(66)

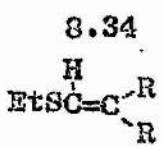


	R^1	R^2	R^3
(66a)	H	H	H
(71a)	H	Me	H
(72a)	Me	H	H
(73a)	Me	H	Me

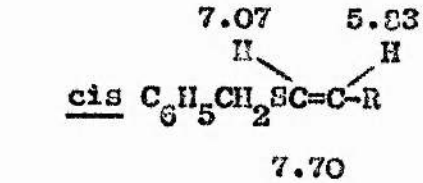
adjacent protons on what was C-4 and C-5 of thiazole since the coupling constant between these protons is in agreement with two vinylic protons on adjacent carbon atoms. The position of the signal (1H) at δ 8.13 requires the proton to be at what was C-2 of thiazole and thus be vinylic, since it does not agree with the chemical shift (δ 5.08) of the proton on the tetrahedral carbon atom in the model compound 2,3-dimethyl-2,3-dihydrobenzothiazole (62). The model compounds dimethyl-2-methylthiophene-3,4-dicarboxylate (67), dimethyl ethylthiomethylenemalonate (68) and cis and trans methyl-β-benzylthioacrylate (69) and (70) were prepared. The chemical shifts of the corresponding protons (i.e. δ 7.68 of the thiophene diester, δ 8.34 of the thiomethylene-



(67)



(68)



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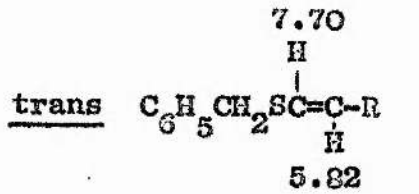
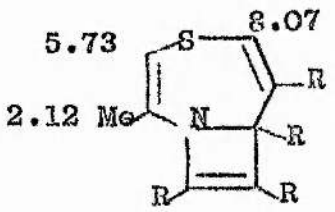


(70)

malonate and δ 7.70 of the trans acrylate) in these model compounds are all in good agreement with the vinylic character of the isolated proton.

The proton magnetic resonance spectrum (Plate 2) of the structure (71) in deuterochloroform showed a group of signals (12H) at δ 3.72 - 3.90 ($4CO_2Me$) a singlet (1H) at δ 8.07, a weakly resolved doublet (3H) at δ 2.12 (CH_3) and a broad unresolved line (1H) at δ 5.73 (vinylic).



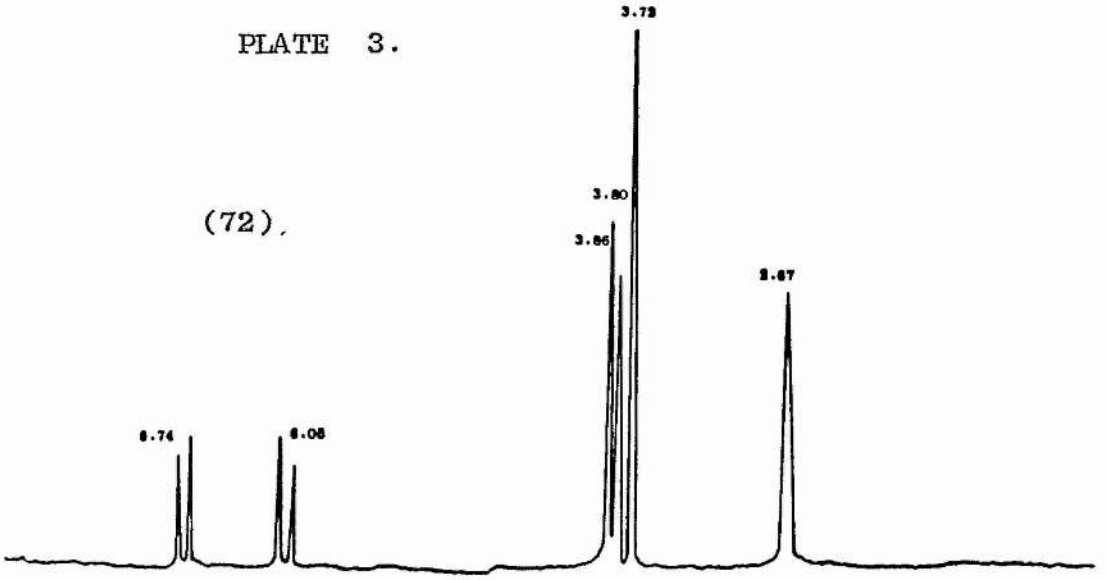
(71)

The signals at δ 2.12 arise from the protons of what was the 4-methyl group of 4-methylthiazole. These protons show allylic coupling (J = 1.3 c./sec.) with the vinylic proton through four bonds. The proton resonance at δ 8.07 requires the proton to be vinylic in good agreement with the corresponding proton in structure (66). The signals of the vinylic protons are slightly upfield compared to those of the corresponding protons in structure (66) due to the shielding effect of the methyl protons (δ 2.12).

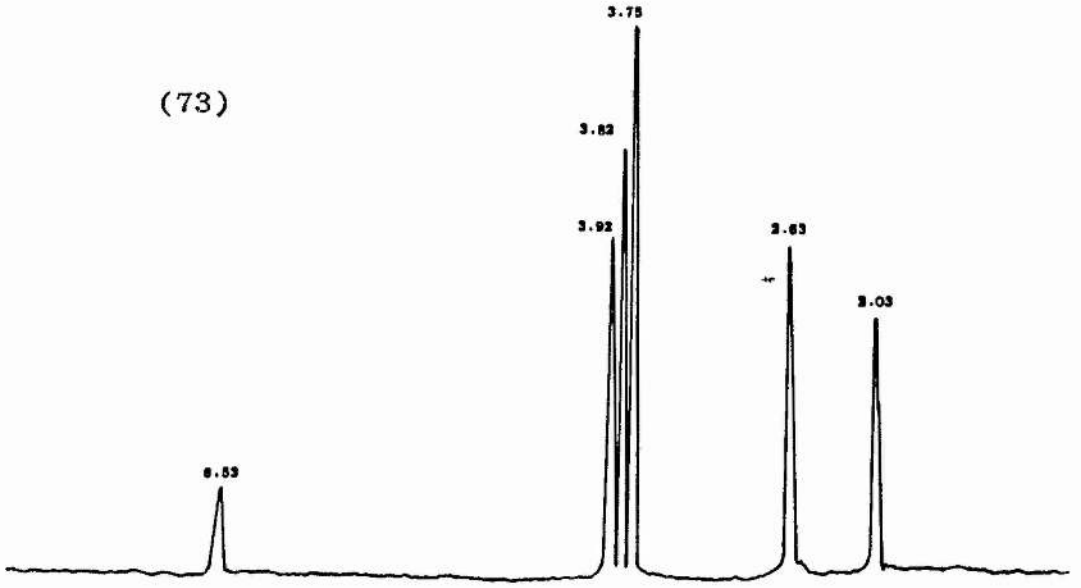
The proton magnetic resonance spectrum (Plate 3) of the structure (72) in deuterochloroform showed a group of signals (12H) at δ 3.72 - 3.86 ($4CO_2Me$), a singlet (3H) at δ 2.67 (CH_3)

PLATE 3.

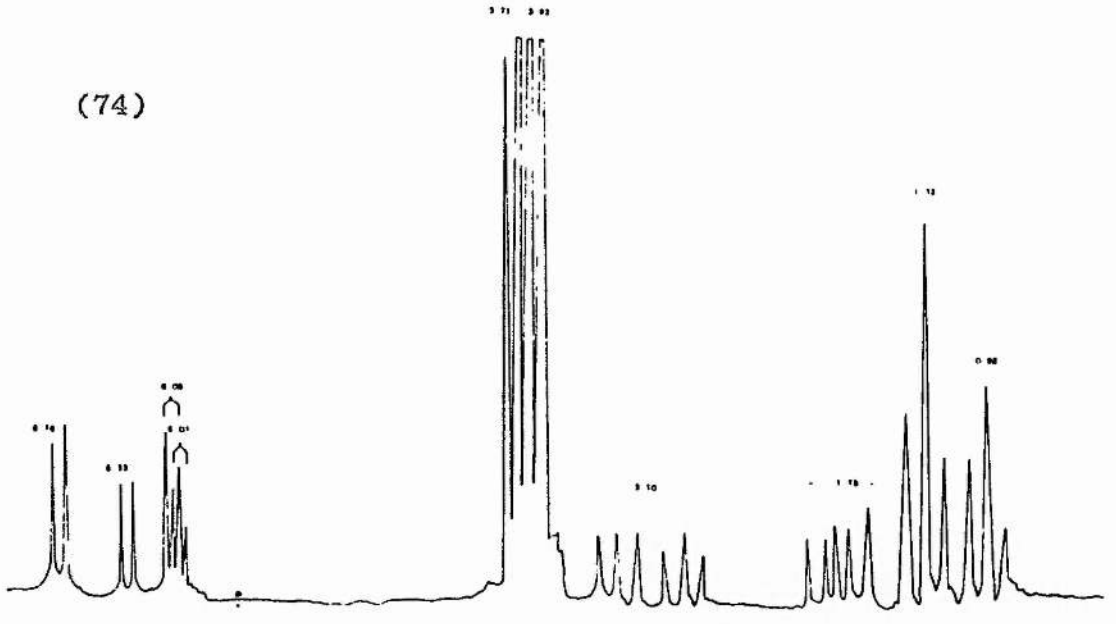
(72).



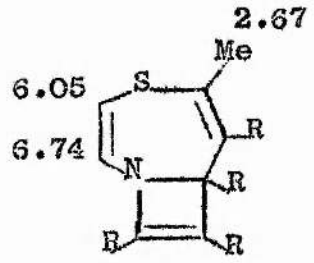
(73)



(74)



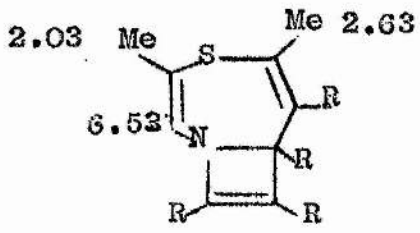
and two doublets of an AB system (2H) centred at δ 6.05 and δ 6.74 (J = 5.0 c./sec.). The lines of the AB system are in the



(72)

same region as those in structure (66) and, by similar reasoning, correspond to the two adjacent protons on what was C-4 and C-5 of 2-methylthiazole. The signal at δ 2.67 arises from 3 protons having a chemical shift in close agreement with that of the protons at δ 2.53 of the vinylic methyl group in the thiophene diester (67).

Similarly, the proton magnetic resonance spectrum of the structure (73) in deuterochloroform showed a group of signals (12H) at δ 3.75-3.92($4CO_2Me$), a weakly resolved doublet (3H) at δ 2.03 (CH_3), a singlet (3H) at δ 2.63 (CH_3) and a broad unresolved line (1H) at δ 6.53 (vinylic). Allylic coupling (J = 1.2 c./sec.) is shown between the methyl protons at δ 2.03



(73)

and the vinyl proton at δ6.53. The frequency of the chemical shift of the methyl protons at δ2.63 agrees favourably with that of the corresponding methyl protons in the compound (72) from 2-methylthiazole.

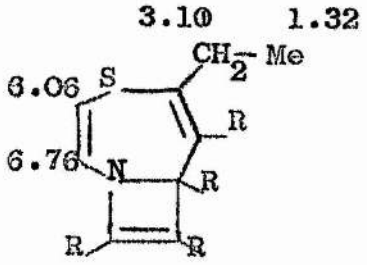
The structures from thiazole, 2-methylthiazole, 4-methylthiazole and 2,5-dimethylthiazole all show a similar deshielding of the group on what was the C-2 position of the respective thiazole, suggesting that this is the result of a structural effect and not simply a substituent effect. Acheson [67] has observed the same effect in the structures isolated from the reaction of thiazole and 4-methylthiazole with dimethyl acetylenedicarboxylate, formulated as our [3,4,0]-bicyclic structures, but does not suggest a reason for the abnormally low resonance positions. Unfortunately, the conditions used in the reaction of 2,4-dimethylthiazole with dimethyl acetylenedicarboxylate did not allow him to isolate a structure corresponding to our [3,4,0]-bicyclic structures. He was not compelled to consider an alternative structure for the products from thiazole and 4-methylthiazole with the ester, since comparison of these low resonance signals could not be made with the signals of the corresponding protons in structures of the type (61) (63) and (64).

No information about the structures (66) (71) (72) and (73) can be obtained from the relative line positions of the ester groups. Consistent patterns observed by Acheson [38] in

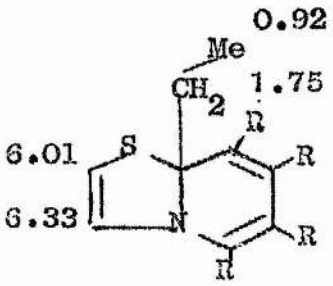
the proton magnetic resonance spectra of the quinolizines were not obtained in these structures. All of the above data indicate that no reaction has taken place at what was the C-4 or C-5 position of the thiazole and that reaction only involves what was the C-2 position.

Both the [5,2,0]-bicyclic and the 1,4-thiazonine structures fulfil all of the proton magnetic resonance requirements but we propose the [5,2,0]-bicyclic structure since it would be more stable on stereochemical grounds.

The proton magnetic resonance spectrum (Plate 3) of the structure (74) in deuterochloroform was interesting in that it consisted of two similar spectra, one shifted upfield from the other (See Table 3). A group of signals (24H) appeared at δ 3.71 - 3.92 ($3CO_2Me$), two triplets (6H) at δ 0.92 (CH_3) and at δ 1.32 (CH_3), two quadruplets (4H) at δ 1.75 (CH_2) and at δ 3.10(CH_2) and four doublets of two AB systems (4H) centered at δ 6.01 and 6.33 (J = 4.8 c./sec.); δ 6.06 and δ 6.76 (J = 4.9 c./sec.). The line positions of the AB



(74)



(75)

system δ 6.06 and 6.76 are in good agreement with those in the compound (72) from 2-methylthiazole. It seemed attractive to assign the signals of the other AB system and the upfield ethyl group to those of the corresponding protons in the [3,4,0]-bicyclic structure (75). Structure (74), however, showed only one component by thin-layer chromatography (it melted within a few degrees) and no other structures were indicated.

A more likely explanation for the upfield group of signals is that the structure (74) is forced into another conformation due to steric effects between the bulky ethyl group and the C-1 ester group. Dreiding models show that a number of more favourable conformations exist which can accommodate less steric strain.

The observation that more than one conformation may exist in structure (74) might be further evidence for the fact that a group on what was the C-2 position of thiazole is <u>also</u> vinylic in the [5,2,0]-bicyclic structures.

It was hoped that the corresponding adduct from 2-t-butylthiazole could be prepared in order to see if the same effect would be observed. Unfortunately, 2-t-butylthiazole did not react with dimethyl acetylenedicarboxylate in dimethylformamide or in a number of other solvents under a variety of conditions.

b) <u>Infra-red and ultraviolet spectra</u>

Both the [3,4,0] and [5,2,0]-bicyclic structures showed similar infra-red spectra to those of the analogous 9aH-quinolizines.[32]

There is a considerable difference in the ultraviolet absorption spectra of both structures supporting the assumptions of Acheson [67] and these differences are consistent within a series. The four maxima of the [3,4,0]-bicyclic structures were consistent within 8 mμ. The three maxima of the [5,2,0]-bicyclic structures did not vary significantly from structure to structure (See Table 4).

c) Reactions of the [3,4,0] and [5,2,0]-bicyclic structures.

1) Protonation

The position of protonation of the [3,4,0]-bicyclic structures could not be determined in trifluoroacetic acid since these adducts were found to be unstable in solution, especially if acid was present.

The [5,2,0]-bicyclic structures were more stable to acid. Decomposition was noted only after prolonged boiling in dilute acid. The position of protonation in trifluoroacetic acid was difficult to determine by proton magnetic resonance due to the complexity of the spectrum. It was evident that protonation did not occur on nitrogen since the characteristic broad peak was not observed.

The proton magnetic resonance spectrum of the structure (66:) showed signals of a displaced AB system (2H) downfield at δ 8.61 and 8.96, a broad singlet (6H) at δ 4.18 ($2CO_2Me$) a slightly split singlet (3H) at δ 4.27 (CO_2Me), a multiplet (3H)

at δ 3.70, 3.90, and 4.08 (CO_2Me), a displaced singlet (1H) downfield at δ 10.17 and a poorly resolved singlet (1H) at δ 10.42. It appears that protonation has taken place at an ester group but this is only speculative. The spectrum of the compound (71) from 2-methylthiazole was similar and no definite site of protonation could be established.

2) Attempted Isomerisation

It might be expected that the [3,4,0] and [5,2,0]-bicyclic structures might isomerise to more stable conformations. When samples of the compounds (61), (63), (71) and (74) were sublimed under vacuum (0.1 mm.), the sublimate was found to be entirely starting material by thin-layer chromatography, indicating that these structures are the thermodynamically stable forms.

There were no dramatic changes in the proton magnetic resonance spectrum when samples of the compounds (61) from 2,4-dimethylthiazole and (71) from 4-methylthiazole were observed in deuterochloroform over a range of temperatures from 75.0° - 125.0°.

Interesting information might have been obtained from the proton magnetic resonance spectrum of the compound (74) from 2-ethylthiazole at various high temperatures, but a variable temperature probe, required for this work, was not available.

3) Attempted mercuric acetate desulfurisation

A number of desulfurisations under mild conditions using mercuric acetate were attempted.

When mercuric acetate in glacial acetic acid was warmed with the compound (61), mixtures of polar products were obtained along with starting material. The reaction was not further investigated. The reaction was repeated on the compound (71) and starting material was recovered on "work-up" of the reaction mixture.

4) Reaction with cyanogen bromide

Certain cyclic structures containing nitrogen have been cleaved by treatment with cyanogen bromide.[68, 69] It was hoped that cleavage of a carbon-nitrogen bond might be effected in both compounds (61) and (71). Only a complex mixture of products was observed by thin-layer chromatography of the reaction mixture from the compound (61) and starting material was recovered from the reaction of the compound (71).

The above reactions indicate the relative instability of the [3,4,0]-bicyclic structures.

5) Attempted hydrolysis and decarboxylation

The [3,4,0]-bicyclic structures could not be hydrolysed due to their sensitivity to acids and bases but the compound (71) could be converted to the tetrapotassium salt by boiling under reflux with methanolic potassium hydroxide. The tetraacid formed on acidification of the tetrapotassium salt decomposed on attempted decarboxylation or sublimation.

When the tetrapotassium salt was allowed to stand overnight in a solution of dilute hydrochloric acid (1:1) a dark red

solid was formed which was extremely soluble in polar solvents. It is suspected that this material is polymeric but there was no time to investigate it further.

6) The reaction of tetramethyl-3,8a-dimethyl-8aH-thiazolo[3,2-a] pyridine-5,6,7,8-tetracarboxylate with dimethyl acetylene-dicarboxylate in alcohols.

The [3,4,0]-bicyclic structures gave separate products in ethanol and methanol when heated with dimethyl acetylene-dicarboxylate. The only products that could be isolated were those from the reaction of the compound (61), which is recovered unchanged when warmed with either the ester or methanol (ethanol). Addition of small amounts of acid caused decomposition of the compound without the formation of product. The reaction was nearly complete after the reaction mixture was allowed to stand for four days at room temperature, but could be hastened by boiling the mixture under reflux for 3 hours and then allowing it to stand at room temperature for two days until the product was deposited from solution.

The nearly colourless product from methanol was soluble in a range of polar and non-polar solvents. A positive test for both sulfur and nitrogen were obtained; Ehrlich's test was negative. The proton magnetic resonance spectrum in deuterochloroform indicated that the new adduct was composed of one molecule of starting adduct, ester and alcohol in agreement with the

elemental analysis. The spectrum consisted of a group of signals (21H) between δ 3.59 and 3.85 ($6CO_2Me$, 1 OMe), an upfield doublet (3H) at δ 2.28 (J = 1.3 c./sec.) a singlet (2H) at δ 3.21 and a downfield quadruplet (1H) at δ 6.42 (J = 1.3 c./sec.).

The upfield methyl protons (δ 2.28) and the low field proton (δ 6.42) to which they are slightly coupled are the C-3 methyl and the C-2 proton, respectively, of the original adduct, but the signals have been displaced to lower field. The singlet at δ 3.21 is in the correct region for a signal of a methylene group which may arise from attack of the primary anion, derived from the 8a-methyl group, on a molecule of ester. One of the single peaks of the ester complex at either δ 3.59 or 3.85, could be the signal arising from a methoxy group. It is difficult to rationalize how a molecule of alcohol is incorporated and the structure of this adduct is unresolved.

The [5,2,0]-bicyclic structures were found to be unreactive under similar conditions.

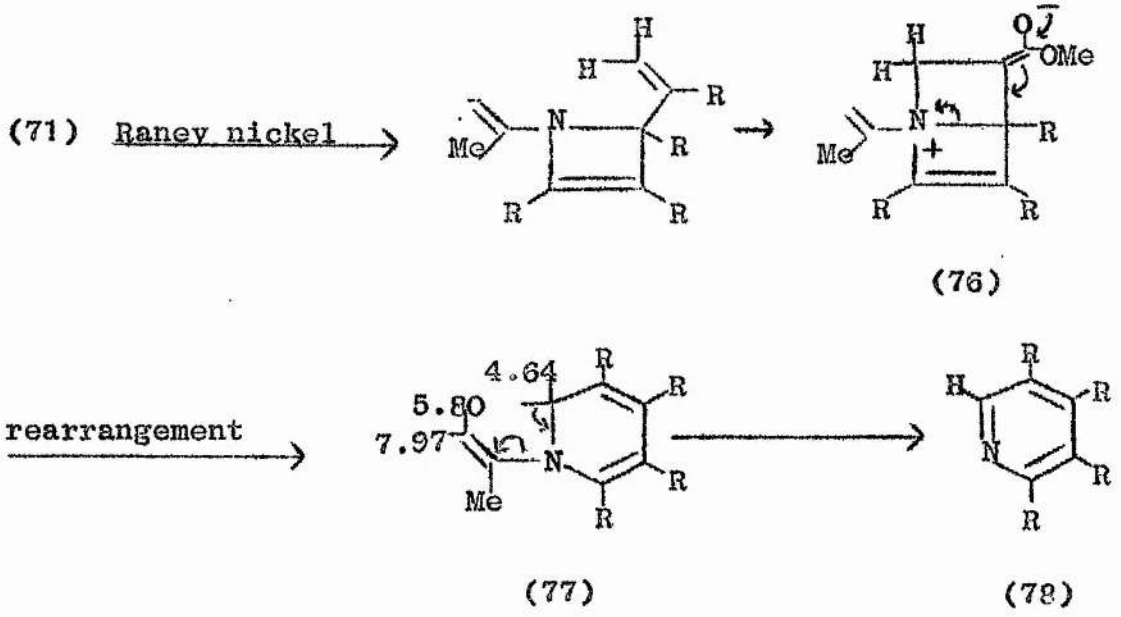
7) Raney nickel desulfurisation

Raney nickel desulfurisation of the compound (61) with active Raney nickel (W-6) catalyst[70, 71] gave a mixture of polar products which were not investigated. A (W-6) catalyst deactivated by boiling under reflux in acetone was prepared according to Rosenkranz;[72] Teich and Curtin[73] and it was hoped that desulfurisation would be effected without

reduction, eliminating unwanted reaction products. It was found that the deactivated catalyst was still too active and the separation of the complex mixture of products was not realised. The reaction was not further investigated.

Raney nickel desulfurisation of the compound (71) with the deactivated catalyst gave a yellow crystalline product which appeared to be homogeneous by thin-layer chromatography but elemental analysis showed it to contain about 2% sulfur. The proton magnetic resonance spectrum in deuterochloroform consists of a group of signals (12H) at δ 3.55 – 3.87 ($4CO_2Me$) and a singlet (3H) at δ 2.15 which is in the same region as that of the methyl group in the starting material. A singlet (2H) at δ 4.64 is in the region of the spectrum which agrees favourably with a methylene signal arising from a group on a carbon atom adjacent to nitrogen.[74] Two weakly split doublets (2H) at δ 5.80 and δ 7.97 (J = 1.6 c./sec.) are the signals assigned to vinylic methylene protons interacting with adjacent methyl protons and the coupling agrees with the allylic constant (J = 0.5 - 2.0 c./sec.),[75] for such an interaction. The dihydropyridine structure (77) fits this information. The spectrum also showed a weak singlet (1H) at δ 9.25, identical to the chemical shift of the C-6 proton in tetramethylpyridine-2,3,4,5-tetracarboxylate (78) which has been formed in isolable amount during peracid oxidation of (71).

Formation of the dihydropyridine (77) presumably involves rearrangement of the intermediate (76) . Aromatisation of the dihydropyridine could form the pyridine tetraester (78).



When the above reaction was performed using the active Raney nickel catalyst an inseparable mixture of the products (77) and (78) was formed. Evidence for this was shown from the increased size of the δ 9.25 signal

The reaction was repeated under reflux for two hours in the hope of obtaining only the tetraester (78) but the same results were obtained.

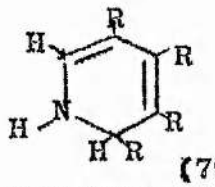
(8) Desulfurisation with zinc and acetic acid

Treatment of the compound (71) with zinc and acetic acid gave a lemon yellow product which was found to be free of sulfur.

The substance was not soluble in deuterochloroform and a proton magnetic resonance spectrum was obtained in trifluoroacetic acid. The spectrum showed a group of signals (12H) at δ 3.88 - 4.10 ($4CO_2Me$), a doublet (1H) at δ 5.68 (J = 4.0 c./sec.), a doublet (1H) at δ 8.24 (J = 6.5 c./sec.) and a broad multiplet (1H) centred at δ 7.65.

The difference in the spin-spin splitting of the pair of signals at δ 5.68 and at δ 8.24 suggests that each proton is coupled in a different manner to the proton of the broad multiplet.

A proton magnetic resonance spectrum of the product in hexadeuterodimethyl sulfoxide might have differentiated between the dihydropyridines (79) and (79a), which have been suggested for the unprotonated product.[76] Unfortunately, the n.m.r. spectrometer



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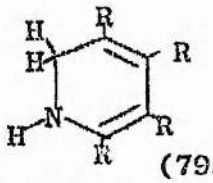
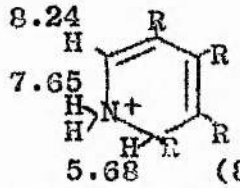


(79a)



(80)

was not operating when a spectrum of the product was to be recorded in hexadeuterodimethyl sulfoxide and there was no time to have the spectrum recorded elsewhere. However the cation (80), from protonation of dihydropyridine (79), satisfies the above proton magnetic resonance data indicating that the dihydropyridine (79) could be the correct structure.

The relative insolubility of this compound in all but polar solvents led one to suspect that it was polymeric. However, the molecular weight was 313 in agreement with the proposed structure.

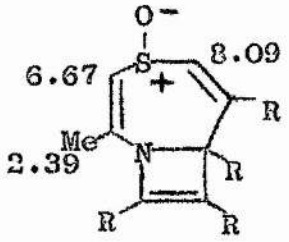
Evidence for loss of the isopropenyl group was demonstrated when the reaction was repeated on the compound (66) . The product exhibited the same melting point, infra-red and proton magnetic resonance spectra as the above product.

9) Oxidation with peracetic acid

The compound (61) gave an inseparable mixture of white and yellow products from peracetic acid oxidation.[77]

The compound (71) gave a light sensitive product on oxidation with peracetic acid. (See Experimental Section). Elemental analysis is in agreement with the empirical formulae $C_{16}H_{17}NO_9S$ for the monoxide. The infrared spectrum showed no intense bands at 950-970 cm^{-1} or 1200-1300 cm^{-1} characteristic of N-oxide functions but the bands of a sulfoxide group at 1058 cm^{-1} and 1064 cm^{-1} were shown to be present. The product was not sufficiently soluble in deuterochloroform for a proton magnetic resonance spectrum determination and hexadeuterodimethyl sulfoxide was employed. The spectrum was interesting in that the signals of the methyl group (δ 2.39) and of the proton (δ 6.67) on what were the C-4 and C-5 positions, respectively, of 4-methylthiazole were both deshielded. This would be expected

if the dipolar form of the sulfoxide is significant, but the position of the proton at δ 8.09, on what was the C-3 position of 4-methylthiazole is unchanged. One would expect this proton to be deshielded in a similar manner if the structure (81) makes a significant contribution.



(81)

10) Oxidation with Pertrifluoroacetic acid

Dropwise addition of one equivalent of pertrifluoroacetic acid [78] to the compound (61) at room temperature gave a mixture of products as shown by thin-layer chromatographic examination of the reaction mixture. A yellow product was isolated at 0° on addition of one equivalent of pertrifluoroacetic acid, (Elemental analysis indicated that it could be the sulfoxide) but not enough material was available for characterisation.

Dropwise addition of one equivalent of pertrifluoroacetic acid to the compound (72) gave a product having an identical melting point to the sulfoxide prepared from the peracetic acid oxidation. On addition of two equivalents of pertrifluoroacetic acid, a mixture of the sulfoxide and a less polar substance was produced which was difficult to analyse. This problem was

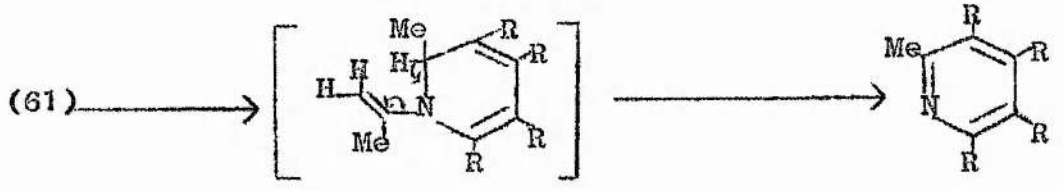
circumvented by isolating the sulfoxide and reoxidising with one equivalent of the peracid. The infra-red spectrum of the product confirmed that it was the sulfone, and not the sulfoxide-N-oxide, since bands at 1120 cm^{-1} and 1321 cm^{-1} were clearly visible. No N-oxide stretching vibrations at 950-970 cm^{-1} or 1200-1300 cm^{-1} were visible in the spectrum.

When oxidation of the sulfoxide was attempted on a large scale, a white product was isolated in addition to the sulfone. The infra-red spectrum showed bands characteristic of aromatic vibrations at 768 cm^{-1} and 1569 cm^{-1}. The proton magnetic resonance spectrum in deuterochloroform showed a group of signals (12H) at δ 3.96 - 4.00 and a singlet (1H) at δ 9.24 in agreement with the structure for tetramethyl pyridine - 2,3,4,5-tetracarboxylate (78). It might appear that this product is the first real evidence for a [3,4,0]-bicyclic structure, analogous to the proof for ring B in 4H-quinolizines (See Introduction). The [5,2,0]-bicyclic structures could also be cleaved, under these conditions, to intermediates similar to (78) which could subsequently aromatize to the observed tetraester. This is only speculative, however.

11) Oxidative-cleavage with chromic acid

Treatment of the compound (61) with chromium trioxide in glacial acetic acid gave a waxy solid exhibiting an infra-red spectrum similar to that of (78). The proton

magnetic resonance spectrum in deuterochloroform showed a group of signals (12H) at δ 3.91 - 3.99 and an upfield singlet (3H) at δ 2.75. This suggests the structure tetramethyl-2-methylpyridine-3,4,5,6-tetracarboxylate (82) for the degradation product and is presumably formed by cleavage of the carbon-sulfur bond, aromatisation and subsequent cleavage of the carbon-nitrogen bond of the side-chain. The structure of the tetraester (82) was proved by hydrolysis and decarboxylation to α-picoline.



(82)

This is chemical evidence for support of the ring B in the [3,4,0]-bicyclic structures.

Treatment of the structure (71) with chromium trioxide in glacial acetic acid under the same conditions gave a mixture of a yellow and a white product. Extensive chromatography gave the pure yellow material in too low yield for characterisation. It is suggested that the [5,2,0]-bicyclic structures are too stable for complete cleavage under these conditions and the mixture may consist of intermediates and some of structure (78).

All of the above chemical evidence shows that the [3,4,0]-bicyclic structures are indeed less stable than the [5,2,0]-bicyclic structures. The isolation of the pyridine

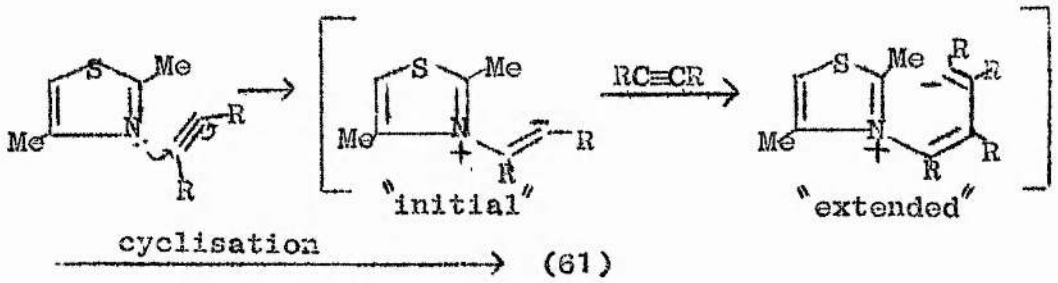
tetraesters and the 1,2-dihydropyridine tetraesters as degradative products certainly lends support for a single [3,4,0]-bicyclic structure. The [5,2,0]-bicyclic structures could also give rise to these degradative products through rearrangement but the spectral evidence from proton magnetic resonance is even more significant, for support of the [5,2,0]-bicyclic structures, since it gives structural information from the molecules observed in their ground state.

d) The mode of formation of the [3,4,0] and [5,2,0]-bicyclic structures.

It is not intended to discuss the mechanisms of formation of the new structures proposed in this thesis in any detail but rather to speculate on the possible routes based on those generally accepted in the analogous quinolizine series. Very little experimental evidence exists in support of the proposed routes.

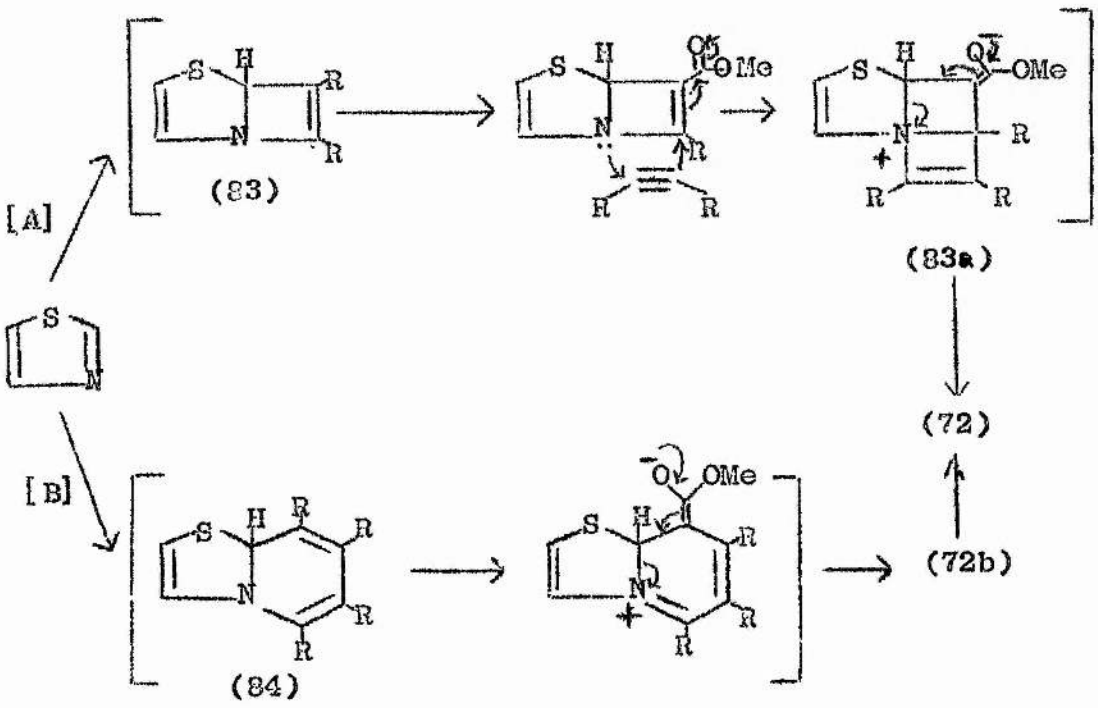
Presumably the mode of formation of the [3,4,0]-bicyclic structures involves the nucleophilic attack of the lone pair of electrons, on the thiazole nitrogen atom, on the triple bond of the ester group - (See Introduction pg. 10). The "initial" zwitterion attacks another molecule of ester and the "extended" zwitterion then cyclises to the [3,4,0[-bicyclic structure (61). The reaction of 2,4-dimethylthiazole with dimethyl acetylenedicarboxylate is given below. Evidence for

the formation of a zwitterion similar to the zwitterion (41)



in the pyridino series, derived by trapping the initially formed zwitterion with carbon dioxide,[50] could not be observed. The reaction of 2,4-dimethylthiazole with dimethyl acetylene-dicarboxylate did not occur at -60°. This was not surprising since the reaction was only moderate at room temperature.

The mode of formation of the [5,2,0]-bicyclic structures, exemplified by the reaction of thiazole, may occur in two ways. In (A), one molecule of the ester may add to the thiazole forming a [3,2,0]-bicyclic system (83) which may add a second molecule of ester and then rearrange to the [5,2,0]-bicyclic structure (72) as shown below.



In (B), a more likely route, two molecules of the ester may add to the thiazole through an extended zwitterion which may cyclise to the transient [3,4,0]-bicyclic system (84). The structure may then rearrange to the more stable structure (72) through the 1,4 thiazonine structure (72b). There is some experimental evidence that could be used in support of mechanism (B). Traces of a product (not enough to isolate on the 20 mmole scale) having similar polarity to the [3,4,0]-bicyclic structures were observed by thin-layer chromatography of the reaction mixture of 2,5-dimethylthiazole with dimethyl acetylenedicarboxylate. The intermediate (84) may be stabilized enough by an alkyl group at what was the 5-position of the thiazole to be isolated. The pathways (A) and (B) are only speculative, however.

[c] The addition of 2-alkylthiazoles to dimethyl acetylenedicarboxylate in methanol or acetonitrile

The addition of 2-alkylthiazoles to dimethyl acetylenedicarboxylate in methanol or acetonitrile gave a class of adducts formulated as the [3,5,0]-bicyclic structures, 5,6-dihydrothiazolo[3,2-g]azepines, which could be isolated by chromatography using polar solvents, after traces of less polar material were first removed. The product from 2-ethylthiazole was best obtained using acetonitrile as solvent.

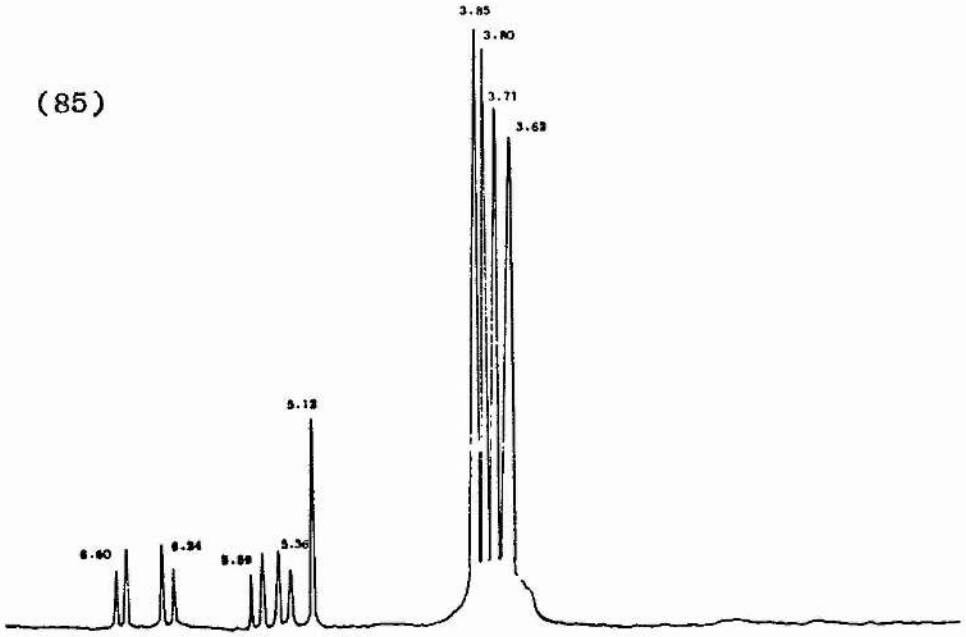
a) Proton magnetic resonance

Proton magnetic resonance spectroscopy was also used for elucidation of the structures of these adducts.

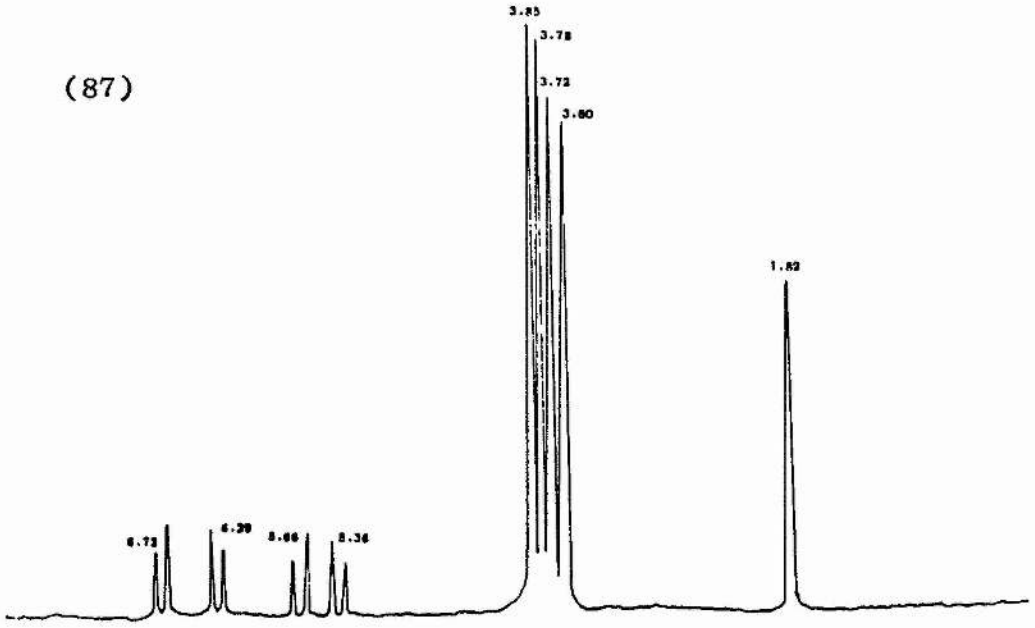
The proton magnetic resonance spectrum (Plate 4) of the structure (85) from 2-methiazole in deuterochloroform showed a group of signals (12H) at δ 3.62 - 3.85 ($4CO_2Me$), two doublets of an AB system (2H) centred at δ 6.24 and 6.60 (J = 4.6 c./sec.), two doublets of a second AB system (2H) centred at δ 5.36 and 5.59 (J = 5.3 c./sec.), and a sharp singlet (1H) at δ 5.12. Since no methyl signal was evident in the spectrum, it was clear

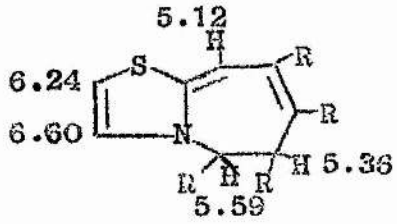
PLATE 4.

(85)

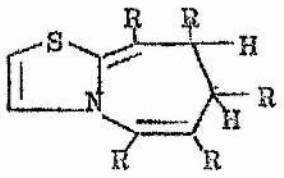

3.85
3.80
3.71
3.63
5.13
6.60
6.24
5.89
5.36

(87)


3.85
3.78
3.72
3.80
1.82
6.72
6.29
5.86
5.36



(85)

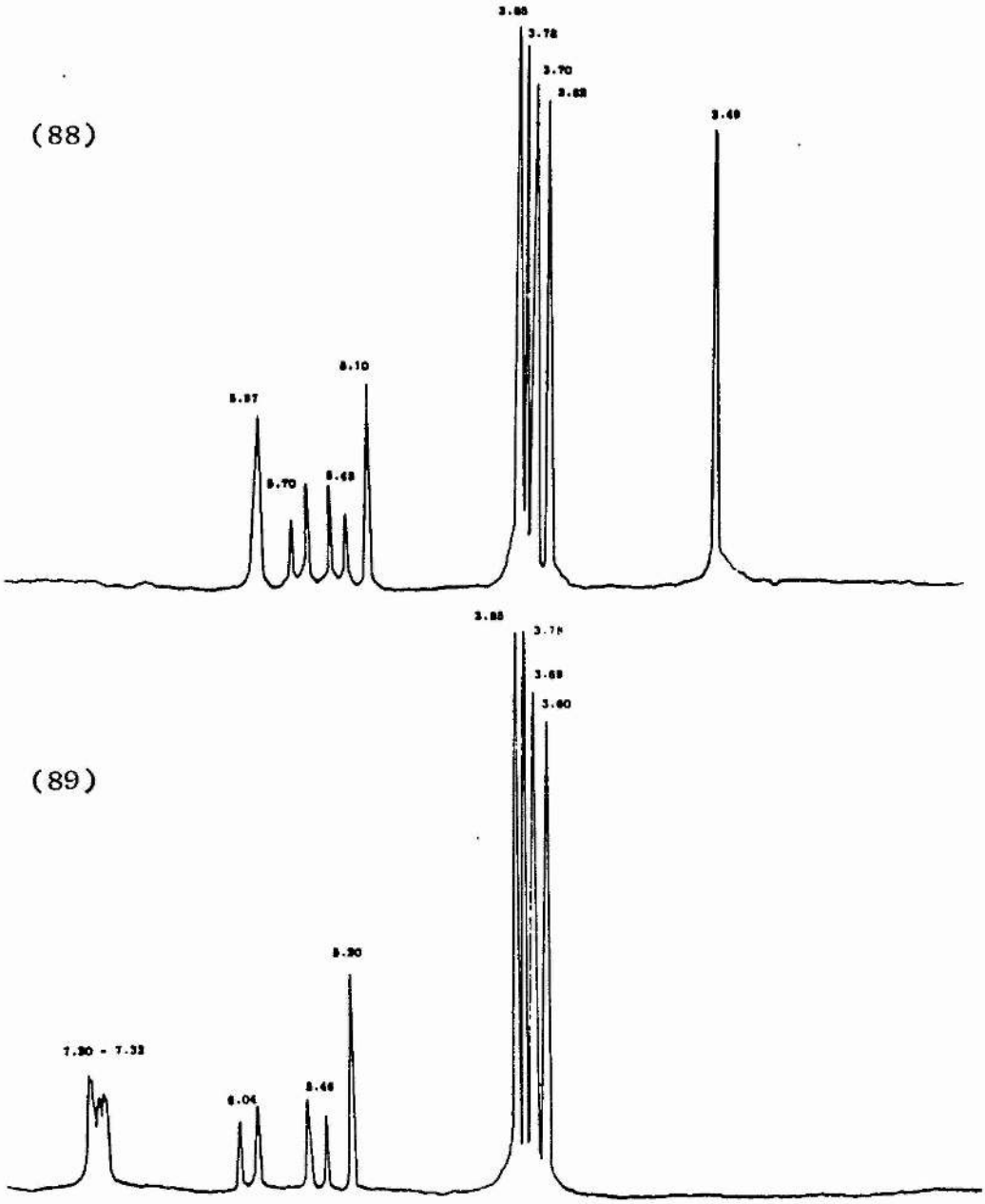


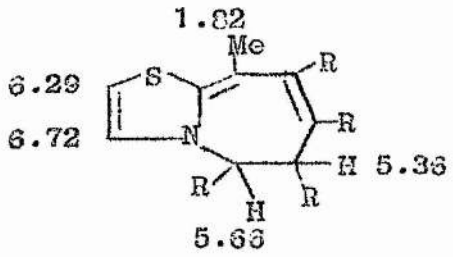
(86)

that reaction had taken place at what was the C-2 methyl group of 2-methylthiazole. The sharp singlet at δ 5.12 indicated that the corresponding proton was vinylic. The position of the signals of the AB system (δ 6.24 - 6.60) required that both protons be on a double bond and the signals were assigned to the thiazole ring protons. The protons of the remaining AB system (δ 5.36 - 5.59) must reside on tetrahedral carbon atoms in the newly formed ring. The two structures (85) and (86) satisfy these requirements but since the single proton was unsplit the structure (86) must be ruled out leaving structure (85) as the only one having the correct bond distribution.

The proton magnetic resonance spectrum of the structure (87) in deuterochloroform showed a group of signals (12H) at δ 3.60 - 3.85 ($4CO_2Me$), two doublets of an AB system (2H) centred at δ 5.36 and 5.66 (J = 5.5 c./sec.), two doublets of a second AB system (2H) centred at δ 6.29 and 6.72 (J = 4.5 c./sec.), and a sharp singlet (3H) at δ 1.82 (CH_3)

PLATE 5.


(88)
3.88
3.78
3.70
3.68
3.49
8.10
8.07
8.70
8.48
(89)
3.88
3.78
3.68
3.60
8.30
7.30 - 7.33
8.04
8.46

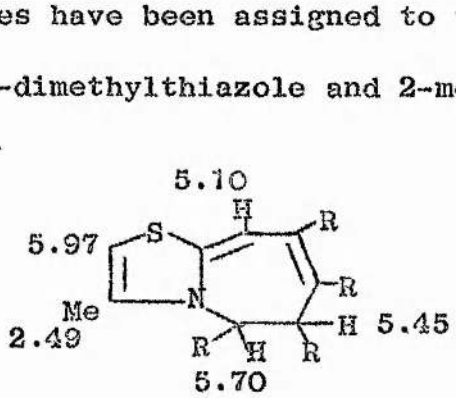


(87)

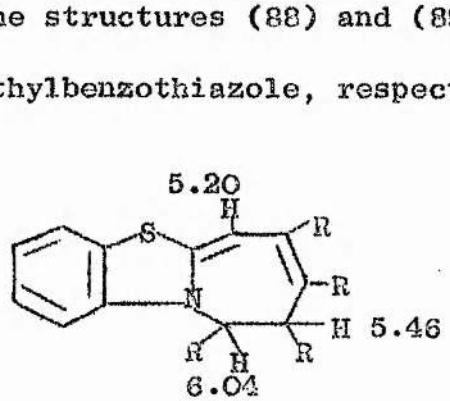
The methylene group of the 2-ethyl substituent must have reacted since no methylene or methine signals are present. The methyl signal is unsplit indicating that the corresponding protons must be vinylic. The lines of both AB systems are assigned using similar reasoning as above.

The structure (87) satisfies the above data and the signal of the methyl protons (δ 1.82) gives added evidence that the signal at δ 5.12 in structure (85) has been correctly assigned.

On the basis of similar reasoning analogous [3,5,0]-bicyclic structures have been assigned to the structures (88) and (89) from 2,4-dimethylthiazole and 2-methylbenzothiazole, respectively.



(88)

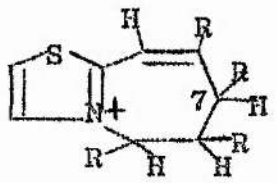


(89)

b) Infra-red and ultraviolet spectra

The [3,5,0]-bicyclic structures showed infra-red spectra consistently similar to those of the [3,4,0] and [5,2,0]-bicyclic structures but were not characteristic enough to be of any value.

The ultraviolet absorption spectra show that there is more extended conjugation in the [3,5,0]-bicyclic structures than in the [3,4,0]-bicyclic structures (Table 4). Two maxima appeared in all spectra, one broad in the ultraviolet region and one maximum in the visible region. Acheson [67] has shown that the ultraviolet absorption spectrum of the structure (89) consists of only two inflections together with the corresponding maximum in the visible region. Only the single maximum in the visible region was observed in structure (88). The ultraviolet absorption maxima are shifted to longer wavelength when the spectra of methanol/perchloric acid (20% v/v) solutions of the [3,5,0]-bicyclic structures are determined (See Table 4). This shows that conjugation has been extended in the cation (90) and that protonation must occur at position C-7 as shown.



(90)

c) Reactions of the [3,5,0]-bicyclic structures

1) Protonation of compound (88).

Protonation of the [3,5,0]-bicyclic structures in trifluoroacetic acid was reversible. As with the [3,4,0]-bicyclic structures the position of protonation was difficult

to determine by proton magnetic resonance due to the complexity of the spectrum. There was no evidence of protonation on nitrogen since no broad peak was observed. The proton magnetic resonance spectrum of the compound (88) in trifluoroacetic acid showed a displaced singlet (3H) at δ 2.78 (CH_3), a singlet (1H) at δ 3.74, a group of signals (12H) at δ 3.92, 3.88, 3.95 and 4.08 ($4CO_2Me$), a multiplet (1H) centred at δ 4.92, a broad singlet (1H) at δ 5.25, a doublet (1H) centred at δ 6.42, and a multiplet (2H) centred at δ 8.08. It is difficult to make any assignments from this spectrum other than the fact that protonation at position 7 is likely, in agreement with ultraviolet spectral evidence, since the characteristic AB system of the 7-membered ring has vanished. It appears that protonation at an ester group has also taken place (this is more evident in the spectrum of structure (87) where anomalous signals appear with those of the ester groups).

When the spectrum of the compound (88) was determined in deuterotrifluoroacetic acid, the original AB system (2H) reappeared at δ 4.94 and δ 6.46 (J = 5.2 c./sec.), as sharp doublets. This indicates that the added proton at position 7 is rapidly exchanging. The broad singlet at δ 5.25 (assigned to the vinylic proton of the 7-membered ring) is diminished in intensity indicating slow exchange of this proton for deuterium.

2) <u>Attempted isomerisation of compounds (87) and (88).</u>

When samples of the compounds (87) and (88) were

sublimed under vacuum (0.1 mm.), the sublimate was found to be entirely starting material by thin-layer chromatography and mixed melting point with the starting material.

3) Attempted hydrolysis and decarboxylation of compound (88).

The attempted isolation of the tetraacid led only to decomposed material similar to what was obtained from the compound (72). A polymeric material was also obtained, in a similar manner, when the tetrapotassium salt was treated with dilute hydrochloric acid. It appears that both the [3,5,0] and [5,2,0]-bicyclic structures require the ester groups for stability.

4) Attempted mercuric acetate desulfurisation of compound (88)

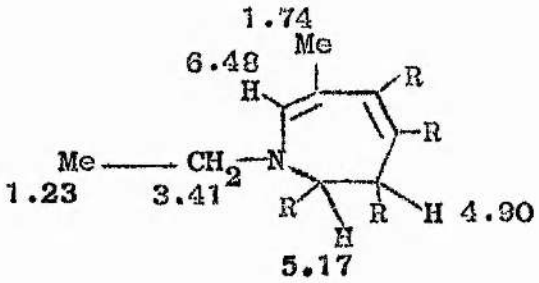
Mercuric acetate desulfurisation of the compound (88) gave only a complex mixture of polar products and the method was not further investigated.

5) Attempted Raney nickel desulfurisation of compound (87)

Attempted Raney nickel desulfurisation of the compound (87) with deactivated Raney nickel (W-6) catalyst [72] was unsuccessful when performed (1) at room temperature and (2) under reflux in a (1:1) mixture of acetone and ethanol. Only starting material could be isolated from the reaction mixtures.

When desulfurisation of compound (87) was performed with Raney nickel (W-4) catalyst,[79] a product was isolated as lime-

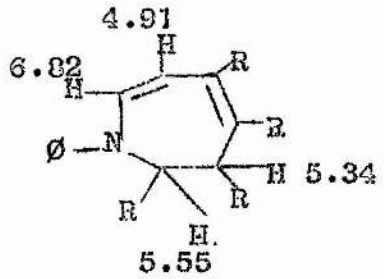
yellow prisms which gave a negative test for sulfur. The proton magnetic resonance spectrum showed a group of signals (12H) at δ 3.63 - 3.80 ($4CO_2Me$), a triplet (3H) centred at δ 1.23 (CH_3), a quadruplet (2H) centred at δ 3.41 (CH_2), a singlet (3H) at δ 1.74 (CH_3), an AB system (2H) centred at δ 4.90 and 5.17 (J = 5.7 c./sec.) and a broad singlet (1H) at δ 6.48. The azepine (91) satisfies these data.



(91)

The lines of the AB system are assigned to the original AB system on the 7-membered ring and are slightly shielded, probably due to the close proximity of the N-ethyl group. The singlet (δ 1.74) is assigned to the vinylic methyl group which is similarly shielded. These methyl protons should be slightly coupled to the adjacent proton (δ 6.48) by 1.5 c./sec. but the splitting is not resolved in this spectrum. The methyl triplet (δ 1.23) and methylene quadruplet (δ 3.41) are assigned to the N-ethyl group.

Acheson has prepared the azepine (92) by Raney nickel desulfurisation of the compound (89) and this is the only structure which accommodates the proton magnetic resonance spectrum (deuterochloroform).[67] The protons on the



(92)

adjacent tetrahedral carbon atoms have a similar coupling constant (J = 6.0 c./sec.) to the corresponding protons of the azepine (91). The chemical shifts are also comparable if one will allow for the deshielding by the N-phenyl group in the azepine (92).

6) Attempted oxidative-cleavage of compound (87)

Treatment of compound (87) with chromium trioxide in glacial acetic acid gave a mixture of polar products and the reaction was not further investigated.

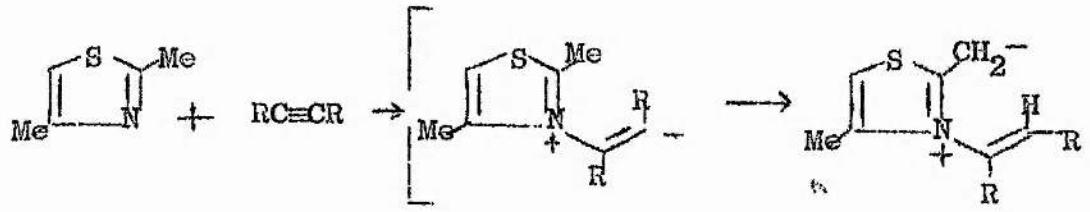
The isolation of the azepine (91), above, together with the proton magnetic resonance assignments are good indications that the [3,5,0]-bicyclic structures are indeed correct.

d) The mode of formation of the [3,5,0]-bicyclic structures

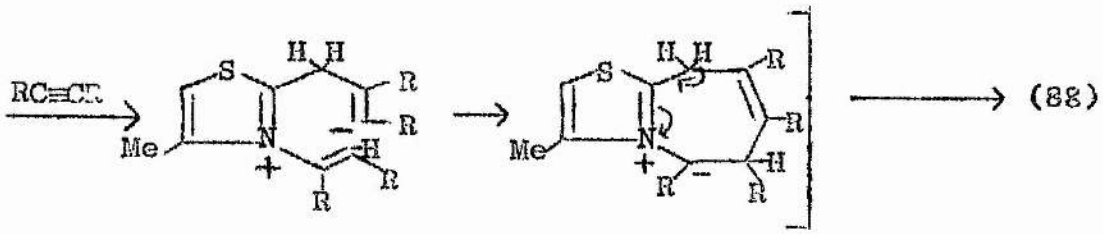
As in the formation of the [3,4,0] and [5,2,0]-bicyclic structures, the mode of formation of the [3,5,0]-bicyclic structures is only speculative.[67]

The reaction of 2,4-dimethylthiazole with dimethyl acetylenedicarboxylate will be taken as an example.

Scheme A. The zwitterion (93) may be formed by the nucleophilic attack of the nitrogen atom of 2,4-dimethylthiazole on the triple bond of a molecule of the ester. The primary carbanion of the zwitterion (93a) then attacks another molecule of ester forming the intermediate zwitterion (94). The azepine (88) is then formed after ring closure and proton transfer. A possible flaw in this mechanism is indicated in that the tertiary carbanion of the



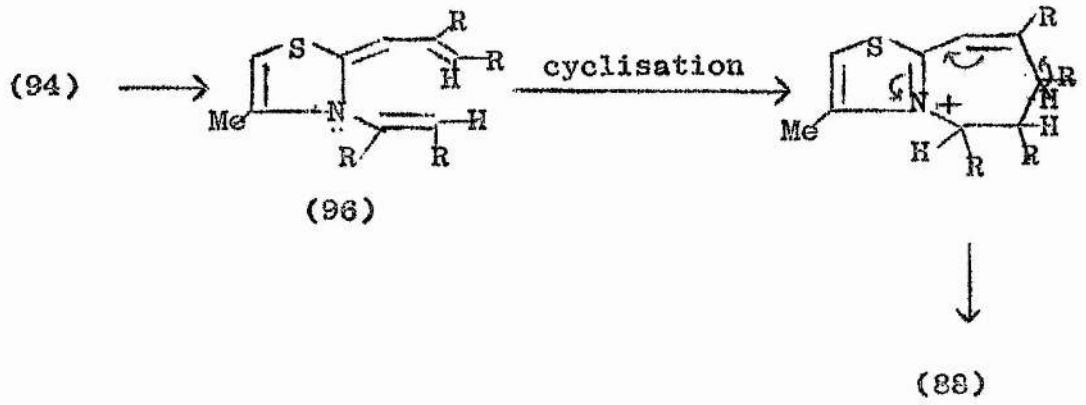
(93) (93a)



(94) (95)

zwitterion (95) would not be expected to be stable enough to give rise to the observed product.

Scheme B A more plausible mechanism might involve cyclisation of structure (96) derived from the zwitterion (94) by protonation of the terminal anion followed by proton transfer to give structure (88).



It is interesting that the formation of azepines is not exemplified by the addition of α-picoline to dimethyl acetylenedicarboxylate.

[D] The addition of thiazole to dimethyl acetylenedicarboxylate in methanol

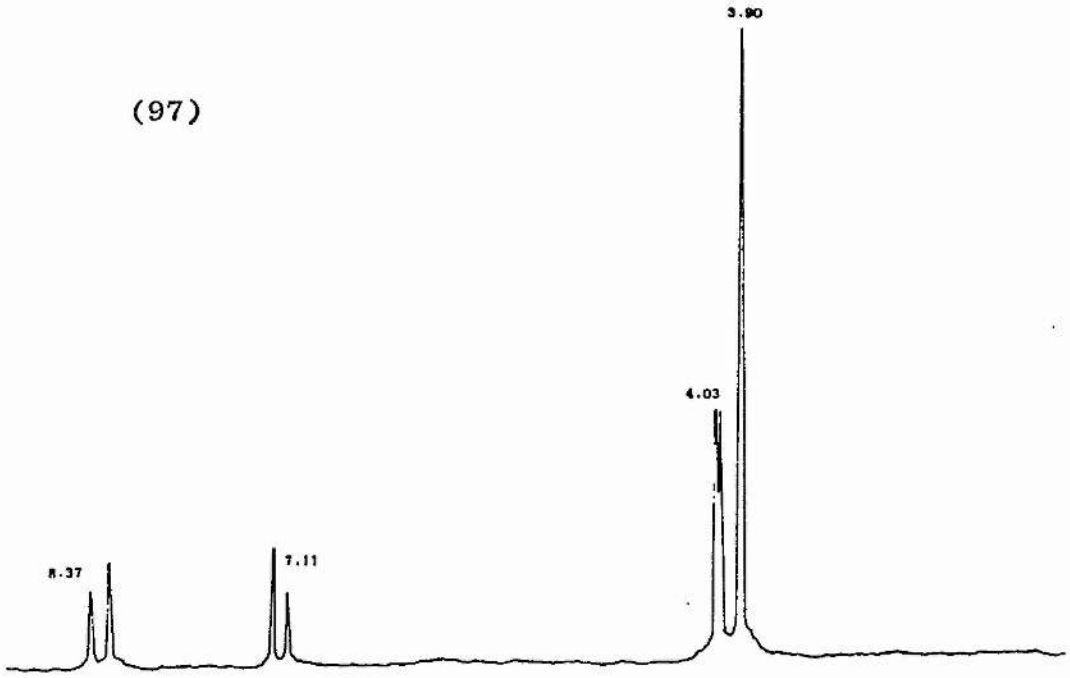
The addition of thiazole to dimethyl acetylenedicarboxylate in methanol gave a colorless adduct formulated as the [3,3,0]-bicyclic structure, trimethyl pyrrolo[2,1-b] thiazole-5,6,7-tricarboxylate which deposited from the reaction mixture as a homogeneous product. The product, in methanol, gave a positive Ehrlich test after being boiled with concentrated hydrochloric acid.

a) Proton magnetic resonance

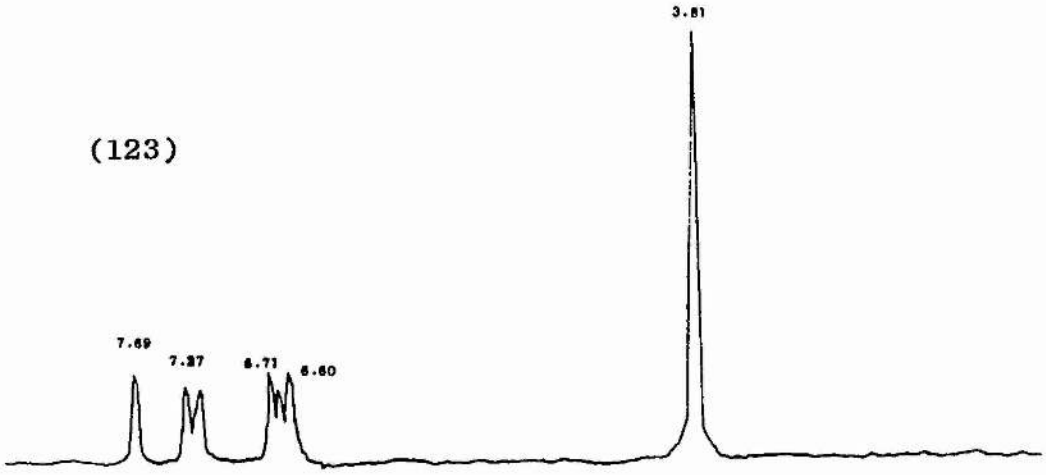
The proton magnetic resonance spectrum of the product in deuterochloroform (Plate 6) showed a singlet (6H) at δ 3.90 ($2CO_2Me$), a singlet (3H) at δ 4.03 (CO_2Me) and an AB pair of

PLATE 6.

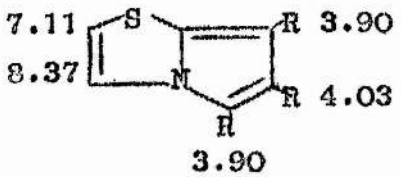
(97)



(123)



doublets (2H) at δ 7.11 and 8.37 (J = 4.5 c./sec.)



(97)

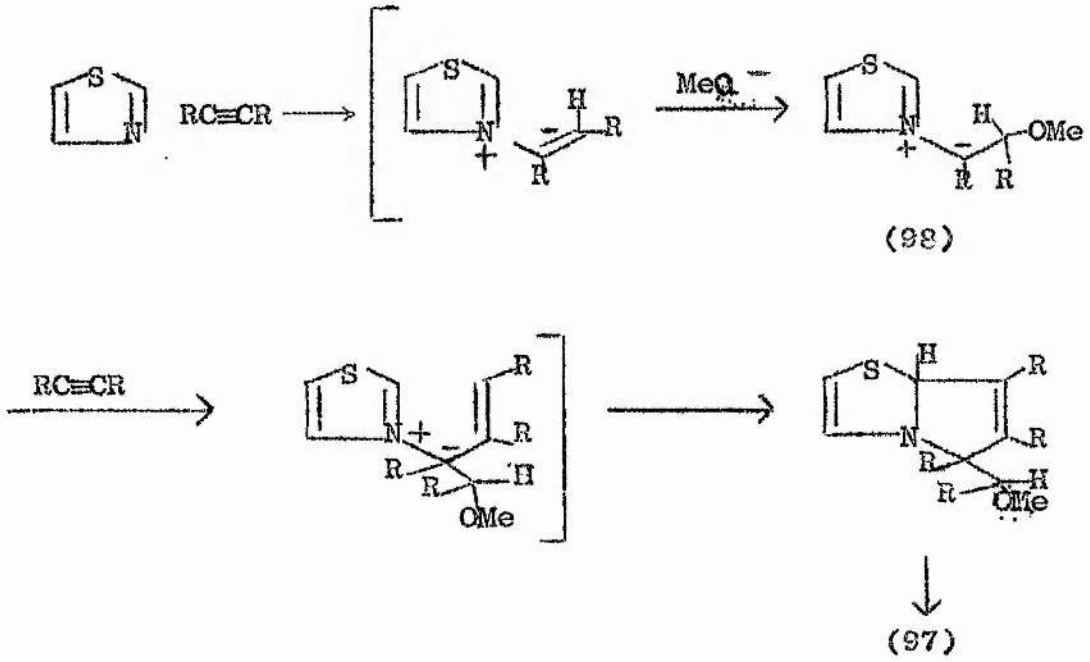
The low field doublet (δ 8.37) must be the proton, of the AB system, adjacent to nitrogen. The ester group at δ 4.03 is assigned to the C-6 position where a deficit of electrons is expected,[4] responsible for the slight deshielding of the ester protons. The low field position of the thiazole ring AB system indicates that a measurable amount of ring current exists in the structure.

Structure (97) satisfies the proton magnetic resonance data.

As desired, the formation of the pyrrolo[2,1-b] thiazole ring system was accomplished by the addition of thiazole to dimethyl acetylenedicarboxylate. Unfortunately the triester (97) is obtained in low yield which seriously limits the practicability of this method as a route to pyrrolo [2,1-b] thiazole itself. Nevertheless, attempts to further characterise this system by hydrolysis and decarboxylation to a 6-carboxylic acid were accomplished and will be discussed in Section (III) dealing with the preparation of pyrrolo[2,1-b] thiazoles.

b) The mode of formation of trimethyl pyrrolo[2,1-b] thiazole-5,6,7-tricarboxylate

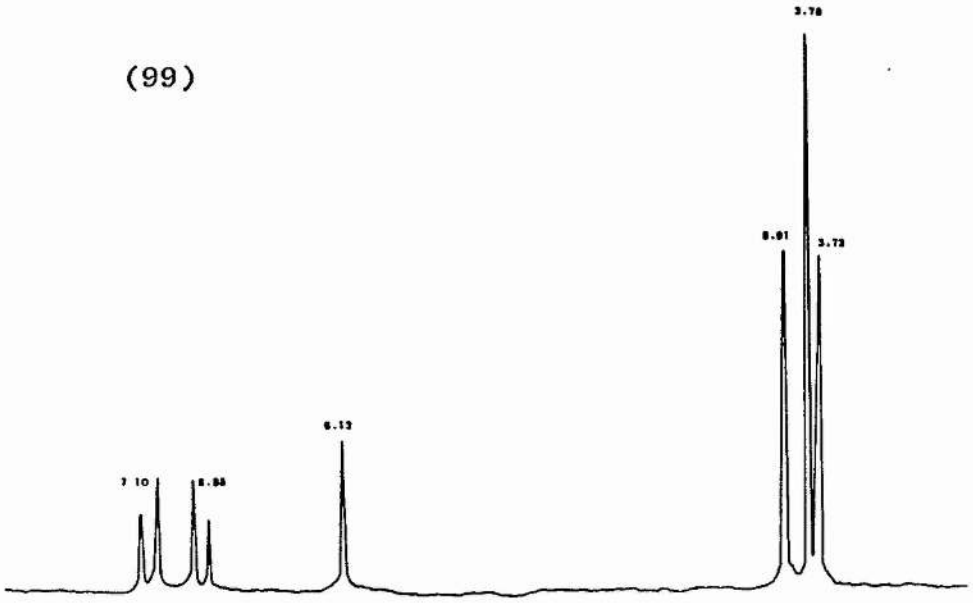
The formation of the triester (97) is probably analogous to the formation of trimethyl indolizine-1,2,3-tricarboxylate (45) from the reaction of pyridine with dimethyl acetylenedicarboxylate [54,55] (See Introduction). The reaction scheme is given below. Initial attack of the thiazole



nitrogen on the ester triple bond is followed by addition of methoxide ion forming the zwitterion (98). Addition of another molecule of ester, cyclisation and subsequent aromatisation would give the triester. It is interesting that only the methoxycarbomethoxymethyl group is lost during aromatisation leading to a single product, in contrast to the indolizine case.

PLATE 7

(99)



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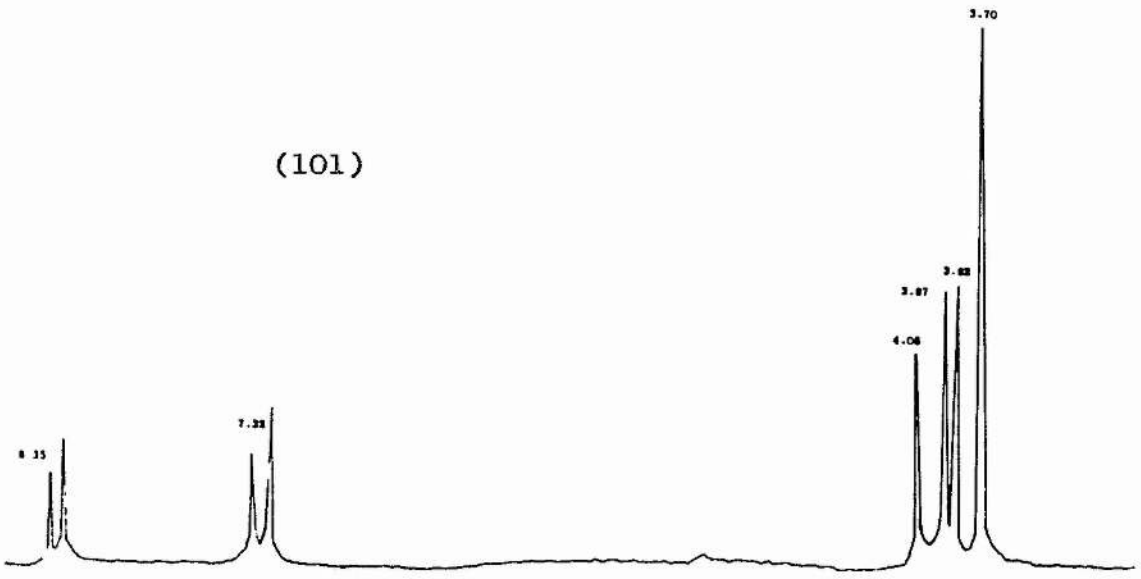


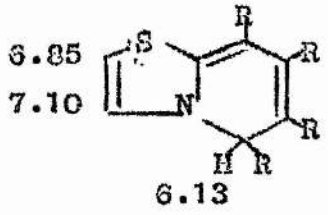
[E] The addition of thiazole to dimethyl acetylenedicarboxylate in diethyl ether at room temperature.

The addition of thiazole to dimethyl acetylenedicarboxylate in diethyl ether at room temperature gave the [3,4,0]-bicyclic structure, tetramethyl-5H-thiazolo [3,2,a] pyridine-5,6,7,8-tetracarboxylate (99), and the [3,5,0] bicyclic structure believed to be pentamethyl thiazolo [3,2,a] azepine-5,6,7,8,9- pentacarboxylate (100) which was fluorescent in solution. Both compounds could be readily isolated, in low yield, by chromatography using ether as an eluent. Some of compound (66) was also obtained.

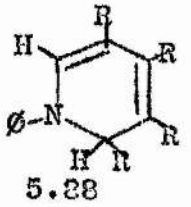
It is interesting that Acheson[67] was not able to isolate the thiazolo [3,2,a] pyridine (99) when the same reactants were mixed at 0° and the reaction allowed to progress at room temperature for 72 hrs.

a) Proton magnetic resonance

The proton magnetic resonance spectrum of the structure (99) in deuterochloroform (Plate 7) showed a group of signals (12H) at δ3.72-3.91 ($4CO_2Me$), two doublets of an AB system (2H) centered at δ6.85 and δ7.10 (J = 4.5c/sec.) and a singlet (1H) at δ6.13. The thiazole ring AB system must have the proton (δ7.11) adjacent to nitrogen compared to the



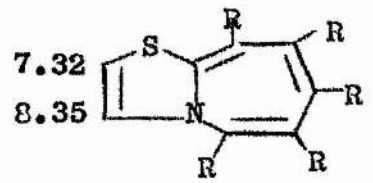
(99)



(100)

corresponding proton (δ 8.37) in the triester (97). The vinylic coupling constant (J = 4.5 c./sec.) is identical to that of the same triester confirming its assignment to a thiazole ring. The dihydropyridine (100) isolated by Acheson [67] could be an acceptable model compound since the proton (δ 5.88) on the tetrahedral carbon atom compares favourably with that of the singlet (δ 6.13) in the corresponding environment in the structure (99).

The proton magnetic resonance spectrum of the structure (101) in deuterochloroform (Plate 7) showed a group of signals (15H) at δ 3.71, 3.71, 3.82, 3.87, 4.05 ($5CO_2Me$) and two doublets of an AB system (2H) centred at δ 7.32 and 8.35 (J = 4.5 c./sec.). The tentative structure (101) also agrees with the proton magnetic resonance and analytical data obtained by Acheson.[67]



(101)

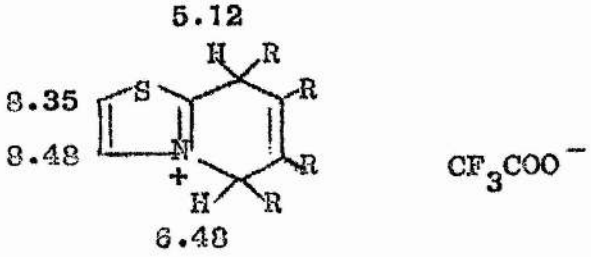
b) Infra-red and ultraviolet spectra

The infra-red spectra of structures (99) and (101) were similar to those of the [3,4,0] and [5,2,0]-bicyclic structures in the 5-7 μ region of the spectrum (See Table 5).

The ultraviolet absorption spectrum of the structure (99) in methanol showed three maxima at 2 48 mμ; 308 mμ and 412 mμ (See Table 4) in contrast to those of the [5,2,0]-bicyclic structures. The ultraviolet absorption spectrum of the structure (101) in methanol showed four maxima at 242 mμ, 317 mμ, 326 mμ and 423 mμ.[67]

c) Protonation

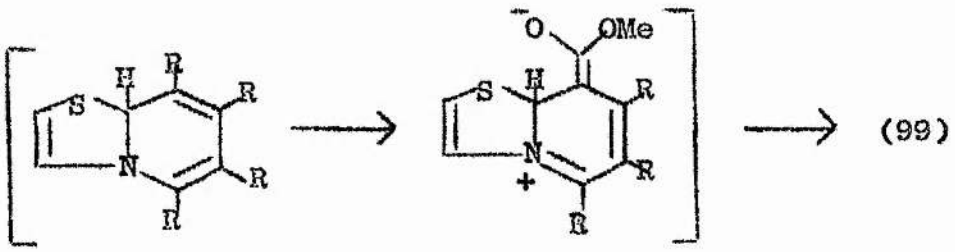
The protonation of the structure (99) was found to be reversible. The proton magnetic resonance spectrum in trifluoroacetic acid showed a group of signals (12H) at δ 3.88 - 4.13 ($4CO_2Me$), two doublets of an AB system (2H) centred at δ 8.35 and 8.48 (J = 4.0 c./sec.), a weakly split singlet (1H) at δ 5.12 and a weakly split singlet (1H) at δ 6.48, both having (J = 1.1 c./sec.). The deshielding of the thiazole ring AB system, the near equivalence of its protons, and the coupling constant (J = 4.0 c./sec.), indicate that a thiazolium structure has been formed. The singlet (δ 6.48) is assigned to the proton at the C-5 position adjacent to nitrogen and its coupling (J = 1.1 c./sec.) suggests coupling through 5 bonds with the proton (δ 5.12) at the C-8 position. A structure which satisfies these requirements is the salt (102)



(102)

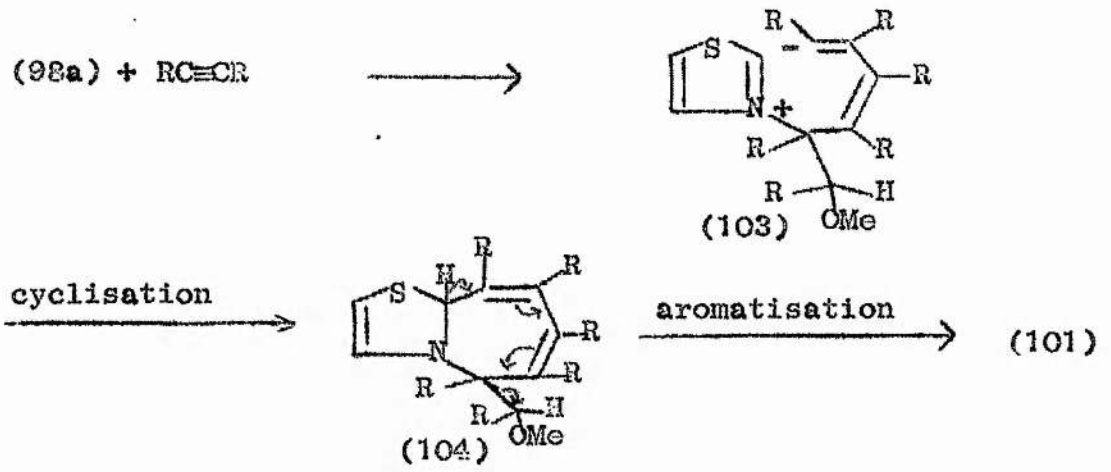
d) The mode of formation of the 5H-thiazolo[3,2-a]pyridine (99) and the thiazolo[3,2-a]azepine (101).

The structure (99) is an isomer of the [5,2,0]-bicyclic structure (66) which is also formed in ether. It could be formed by isomerisation of the intermediate (84), as shown below, to the more stable product. (See Mechanism B, pg. 52).



(84)

The pentaester (101) could be formed according to a scheme analogous to the formation of the triester (97). The zwitterionic intermediate (98a) could attack another molecule of ester, under these conditions, forming the zwitterion (103) which would give the product after cyclisation to the structure (104) and subsequent aromatisation. The reaction scheme is only tentative however.



II. The Addition of Thiazoles to Methyl Propiolate

It was decided to examine the addition of thiazoles to methyl propiolate in order to see if adducts analogous to those formed from dimethyl acetylenedicarboxylate could be prepared.

The reaction conditions employed were the same as those used in the addition of thiazoles to dimethyl acetylene-dicarboxylate. Reactions were allowed to proceed for 96 hours during which time the progress was followed by thin-layer chromatography. Thiazoles were found to be less reactive with methyl propiolate than with dimethyl acetylenedicarboxylate.

All thiazoles studied with the exception of benzothiazole, 2-methylbenzothiazole and 2-t-butylthiazole were observed to react in either dimethylformamide or acetonitrile but the extent of reaction varied markedly. Isolable products could only be obtained from thiazole, 2-methylthiazole and 2,4-dimethylthiazole. Reactions exhibiting a substantial amount of product after four days were repeated and allowed to

react at 100° for six hours on the boiling water bath. Thin-layer chromatography showed less product and more polar material at the origin, indicating that the original conditions (i.e. room temperature) were the more suitable .

2-Ethylthiazole, 2-ethyl-4-methylthiazole and 2,4-dimethylthiazole were also observed to react in methanol but isolable products could only be obtained from 2,4-dimethylthiazole.

No reaction was observed in ether.

[A] The preparation of propiolic acid and its methyl ester

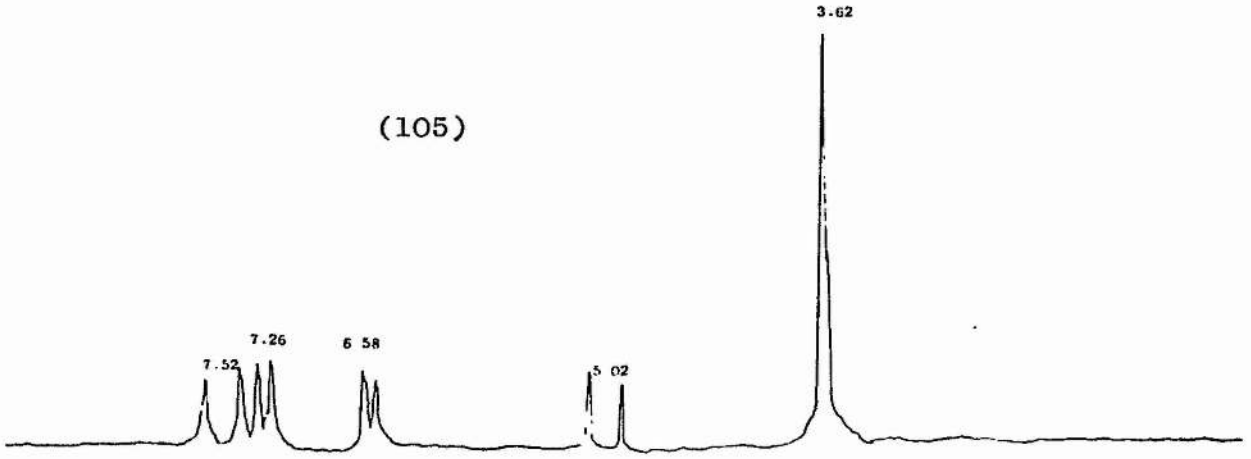
Propiolic acid was prepared by decarboxylation of the monopotassium salt of acetylenedicarboxylic acid according to a method employed by Alder and Stein [80] but using a modified "work-up" procedure.

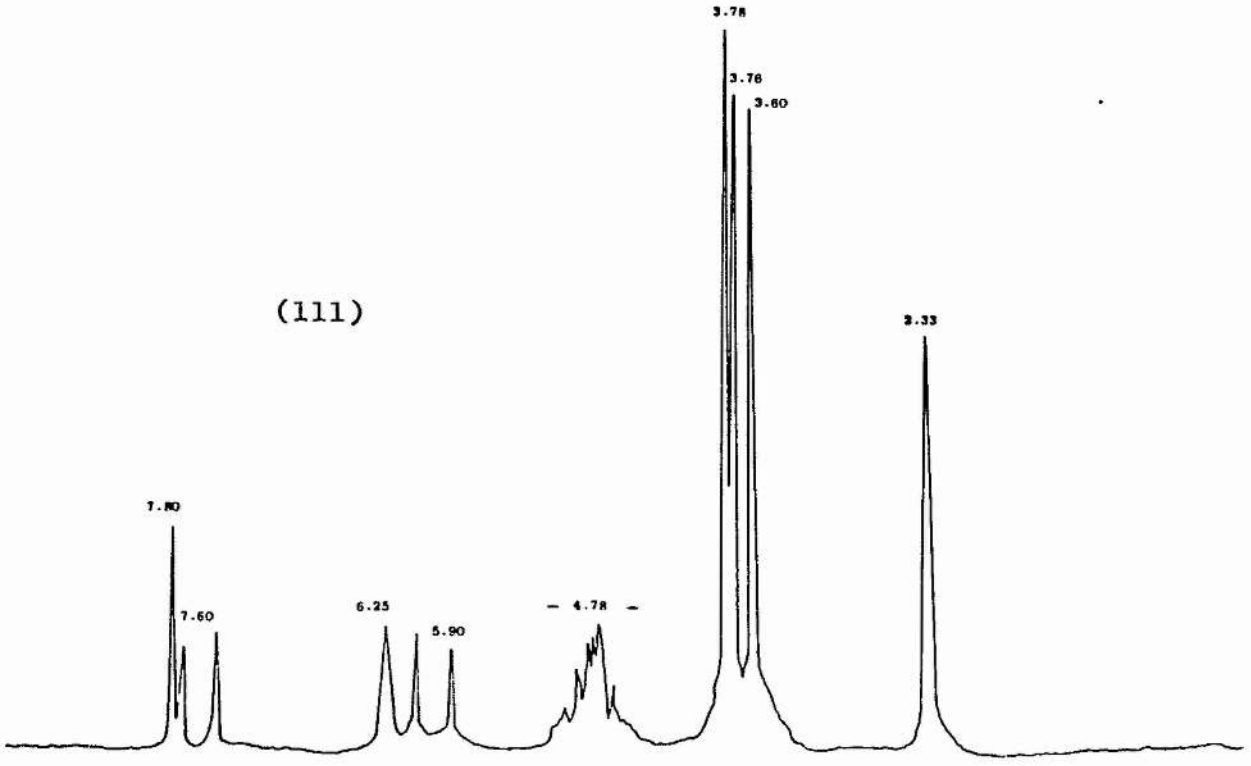
The methyl ester was prepared by treating the acid with a mixture of methanol and sulfuric acid.[81]

[B] The addition of thiazole to methyl propiolate

Thin-layer chromatography showed that the reaction of thiazole (1 mmole) and methyl propiolate (2 mmole) in (1) dimethylformamide and (2) acetonitrile gave an identical product. It was observed that acetonitrile deposited red needles after four days and this solvent was selected for the preparative scale. The red product was found to be unstable in chloroform solution and the proton magnetic

PLATE 8.

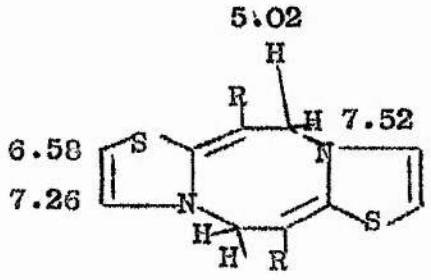




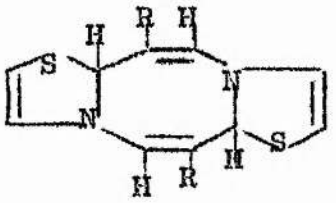
resonance spectrum was recorded in hexadeuterodimethyl sulfoxide

a) Proton magnetic resonance spectrum

The proton magnetic resonance spectrum of the red structure (105) in hexadeuterodimethyl sulfoxide (Plate 8) showed one singlet (6H) at δ 3.62 ($2CO_2Me$), two doublets (2H) centred at δ 5.02 and 7.52 (J = 13.4 c./sec.) and two doublets of an AB system (2H) centred at δ 6.58 and 7.26 (J = 4.4 c./sec.).



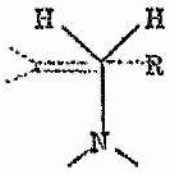
(105)



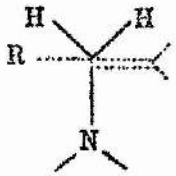
(106)

If one considers initial attack of thiazole on the carbon carrying a proton of the methyl propiolate (See Introduction, pg. 21) then two isomeric structures can be considered that will agree with the above data. The lines of the AB system were assigned to the protons of the thiazole ring by virtue of their chemical shift and coupling constant. The low field doublet (δ 7.52) appears to be a vinylic proton adjacent to nitrogen as in structure (106). The other doublet (δ 5.02) could be the proton on the tetrahedral carbon atom in the same structure. The high coupling constant (J = 13.4 c./sec.) between these protons is not in agreement with this

arrangement and the widely split doublets are assigned to the methylene protons of the structure (105). This assignment is based on the fact that the equivalence of the conformations (107) and (108) of the methylene protons is destroyed by the asymmetry of the rest of the structure.[75]



(107)



(108)

The molecular weight of the compound was determined [82] and found to be 338, in support of the proposed diazocine structure (105). The insolubility of the compound in non-polar solvents also supports a dimeric structure.

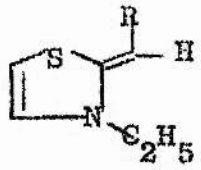
b) Infra-red and ultraviolet spectra

The infra-red spectrum of the structure (105) showed a characteristic spectrum in the 5-7 mμ region associated with ester functions (See Table 5).

The ultraviolet absorption spectrum of the structure (105) in methanol showed three maxima at 238 mμ, 317 mμ and 444 mμ (See Table 4).

It was intended to prepare the chromophoric system (109) in order to compare the ultraviolet absorption maxima with those shown here. If the proposed structure is correct, the

extinction coefficients of the ultraviolet absorption maxima should be twice those of the model system. Unfortunately, there was no time to investigate this topic.



(109)

c) The reactions of the diazocine

1) Attempted protonation

Protonation studies by proton magnetic resonance could not be attempted due to the extreme instability of the diazocine to trifluoroacetic acid.

2) Attempted hydrolysis and decarboxylation

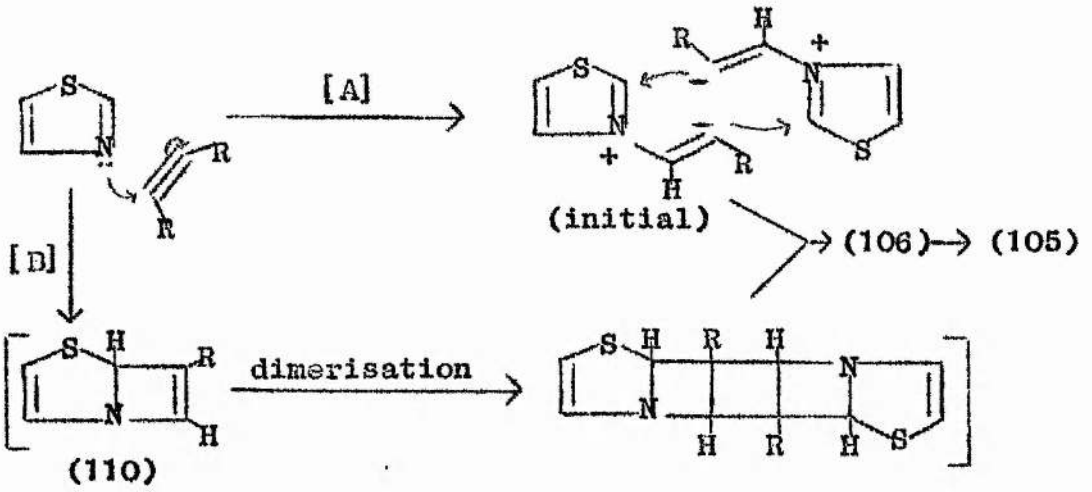
When the diazocine (105) was warmed with a methanolic solution of sodium hydroxide, a strong odour of ammonia was observed and only a colorless gum remained, after "work-up", which would not crystallise. Thin-layer chromatography showed it to consist of a mixture of polar products, close to the origin, and it was not further investigated. Presumably cleavage is facilitated by relief of the strain caused from a twisted conformation. Dreiding models show that there is appreciable distortion associated with the 8-membered ring.

3) Attempted Raney nickel desulfurisation

The attempted Raney nickel desulfurisation of the diazocine[105] using the deactivated (W-3) catalyst[72] gave only a colorless gum which would not crystallise. Thin-layer chromatography showed this to be a mixture of very polar products as was observed from the Raney nickel desulfurisation of the [3,4,0]-bicyclic compound (61). The reaction was not further investigated.

d) The mode of formation of the diazocine

Two routes can be considered for the formation of the diazocine. In (A), nucleophilic attack of the thiazole on the ester (as shown) could give the "initial" zwitterion which then dimerizes to the intermediate (106). Proton transfer would then give the observed product. In (B), the [3,2,0]-bicyclic structure (110), similar to the proposed intermediate (83), (Mechanism (A) page 47) would be expected to dimerize (if formed) and rearrange to the intermediate (106). Both routes are entirely speculative.



[C] The addition of 2,4-dimethylthiazole to methyl propiolate

The addition of 2,4-dimethylthiazole (1 mmole) to methyl propiolate (2 mmole), in various solvents, indicated an appreciable reaction in dimethylformamide, acetonitrile and methanol. Thin-layer chromatography showed the existence of two products except in the case of methanol which gave only the more polar product. It was found that optimum yields of the more polar product could be obtained by performing the reactions in methanol on a scale not exceeding 5 mmoles.

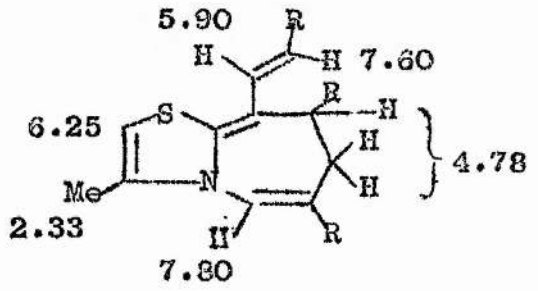
An attempt to obtain the less polar product from the reaction in acetonitrile was not realised.

a) Proton magnetic resonance spectrum

The "polar" product from methanol seemed to be stable in all of the usual solvents and a proton magnetic resonance spectrum was attempted in deuterochloroform (Plate 8). A group of signals (9H) appeared at δ 3.60, 3.76 and 3.78 ($3CO_2Me$), a widely split AB system (2H) at

δ 5.90 and δ 7.60 (J = 16.4 c./sec.), a singlet (1H) at δ 7.80, a singlet (1H) at δ 6.25 which is weakly coupled to a singlet (3H) at δ 2.33 (CH_3) (J = 1.1 c./sec.) and a multiplet (3H) centred at δ 4.78. The protons of the AB system appear to be trans, because of the large coupling constant. The low field signal at δ 7.80 is unsplit indicating that the corresponding proton must be vinylic.

The chemical shift of this proton suggests that it is adjacent to nitrogen. The singlets (δ 6.25) and (δ 2.33) appear to be the respective C-5 proton and C-4 methyl protons of the original thiazole. The group of signals centred at δ 4.78, due to their position and multiplicity, must arise from three protons on adjacent carbon atoms. The proposed structure, in agreement with the data, is the 7,8 dihydro-thiazolo [3,2-a] azepine (111).



(111)

b) Infra-red and ultraviolet spectra

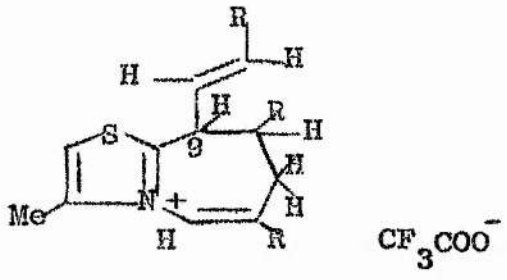
The infra-red spectrum of structure (111) was different from that of the diazocine structure in the 5-7 mμ region of the spectrum and consisted of bands characteristic of ester functions.

The ultraviolet absorption spectrum of structure (111) in methanol showed five maxima at 209 mμ, 242 mμ, 320 mμ, 412 mμ and 439 mμ (See Table 4), indicating a much different system of conjugation in this structure compared to that of the diazocine.

c) Reactions of the 7,8-dihydrothiazolo[3,2-a]azepine (111)

1) Protonation studies

The proton magnetic resonance spectrum of the structure (111) in trifluoroacetic acid was not clear but some information could be extracted. In addition to a group of signals (9H) at δ 3.80, 3.95 and 4.01 ($3CO_2Me$) and the singlet (3H) at δ 2.72 (CH_3), the spectrum was divided into two broad regions; a group of signals (5H) at low field (δ 7.20 - 7.98) and another group of signals (3H) at higher field (δ 4.70 - 5.42). The evidence suggests protonation at C-9 to give the structure (112).



(112)

The group of signals at low field may consist of the vinylic proton adjacent to nitrogen, the thiazole ring proton, the C-9 proton and the protons of the original AB system (on the side chain) to which it is coupled. The group of signals at higher field may consist of the protons on the adjacent tetrahedral carbon atoms which are further coupled to the C-9 proton. The position of the signals at higher field can be explained since the respective protons are insulated from the positively charged nitrogen atom.

The proton magnetic resonance spectrum of structure (111) in deuterotrifluoroacetic acid did not show a simplified spectrum.

2) Attempted Raney nickel desulfurisation

The attempted Raney nickel desulfurisation of the structure (111) using the deactivated (W-6) catalyst [72] was unsuccessful, and only colorless polar products were produced, as in the corresponding Raney nickel desulfurisation of the diazocine (105).

3) Attempted oxidative cleavage using chromic acid

Oxidative-cleavage of structure (111) using chromic acid was also unsuccessful and only a mixture of colorless polar products near the origin could be isolated.

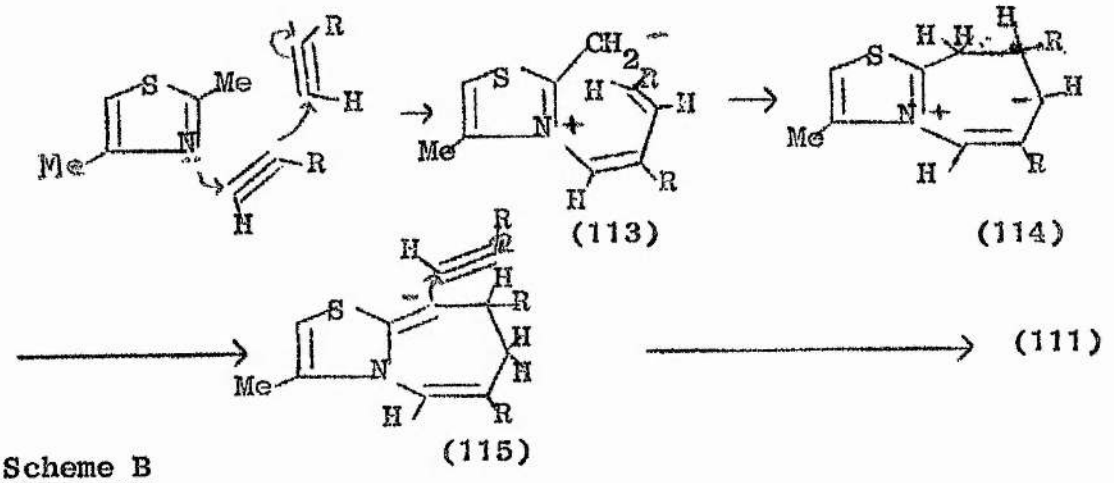
No other reactions were attempted.

d) The mode of formation of 7,8 dihydrothiazolo[3,2-a] azepines

Three possible routes to the 7,8 dihydrothiazolo [3,2-a] azepine ring systems, prepared from the addition of 2,4-dimethylthiazole to methyl propiolate, can be considered. The mechanisms discussed are only tentative and others might also be considered.

Scheme A

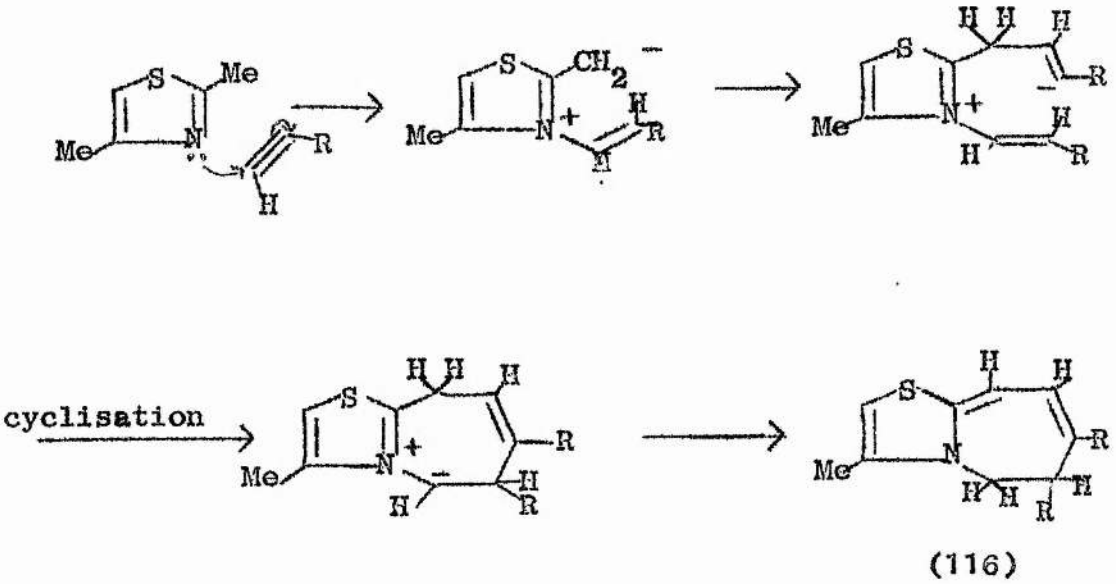
The route to the proposed structure (111) may involve attack of the primary anion of the zwitterion (113) on the terminal carbon atom, to give zwitterion (114). Proton transfer would then give the intermediate (115). The C-9 proton possesses enhanced enamine reactivity since there is no ester group at the C-7 position through which it can conjugate to give it stability as is demonstrated in the isolable 5,6-dihydro-thiazolo[3,2-a] azepines. Addition of a third molecule of ester might be expected at this position giving rise to the observed product. There is no evidence, however, for the existence of the intermediate (115).



(113) (114) (111) (115)

Scheme B

The route analogous to the formation of 5,6-dihydrothiazolo[3,2-a]azepines (See page 61) would give the structure (116), which should be isolable.



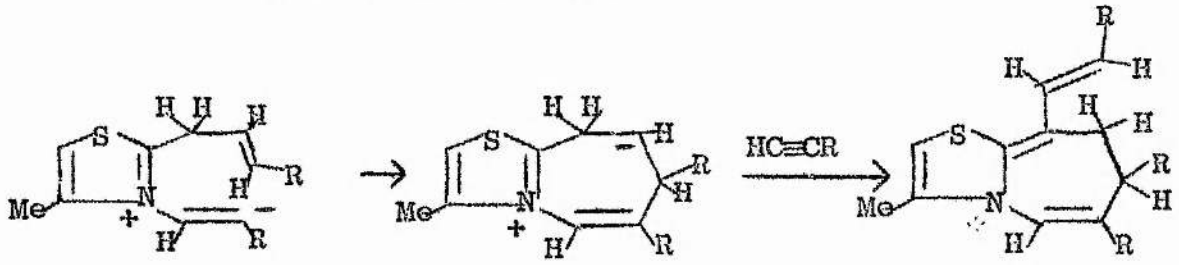
(116)

The proton magnetic resonance spectrum should show signals assigned to only two ester groups since addition of a third molecule of ester would not be expected to occur here. The signal at δ 7.80 arising from a vinylic proton adjacent to

nitrogen should not be observed if this structure is correct. The proton magnetic resonance spectral data rule out this mechanism.

Scheme C

The third possible route involves cyclisation of the zwitterion (117), similar to the zwitterion (94), (See page 61) to give the zwitterion (118). After proton transfer, the zwitterion (118) presumably adds another molecule of ester to give the product (119). This structure might satisfy the proton magnetic resonance data but can be eliminated on mechanistic grounds, since one would not expect the zwitterion (117) to be formed if initial attack by nitrogen on a molecule of ester is indeed the first step.



(117) (118) (119)

[D] The addition of 2-methylthiazole to methyl propiolate

Thin-layer chromatography indicated that the addition of 2-methylthiazole (1 mmole) to methyl propiolate (2 mmole) gave one major product in both acetonitrile and dimethylformamide. Two methods of "work-up" were employed.

1) Extraction of the residue with $1\bar{N}$ and $2\bar{N}$ hydrochloric acid gave only a few milligrams of material.

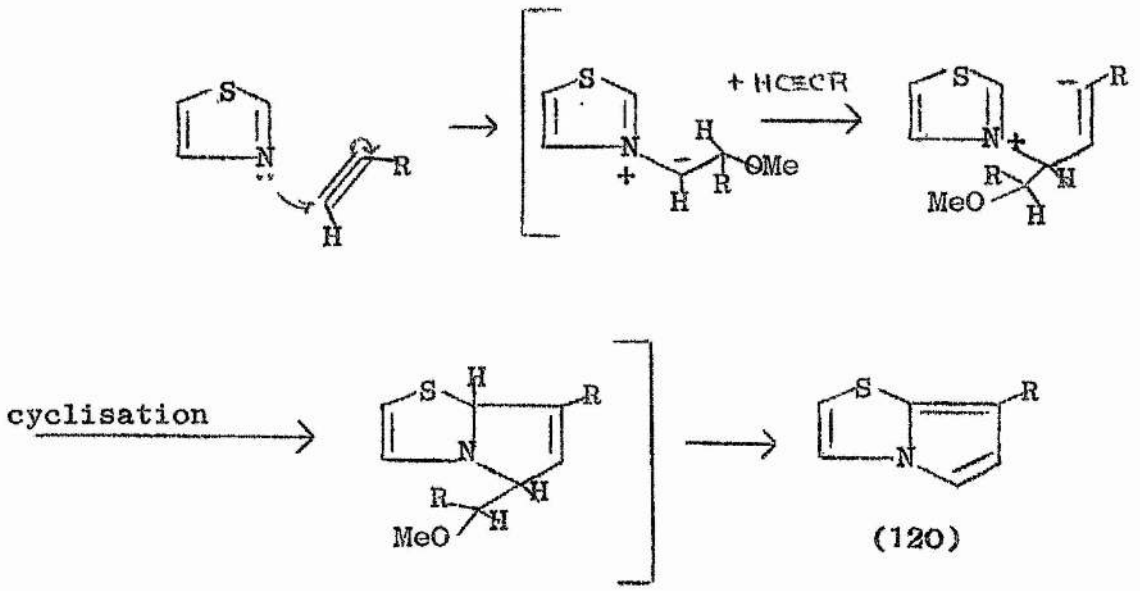
2) Chromatography of the residue did not separate a greater amount of product and characterisation of this compound could not be accomplished.

a) Infra-red spectrum

The infra-red spectrum of the product showed a substantial difference in the 5-7 micron region compared with the structure (112). There was not enough material available for the determination of the ultraviolet absorption spectrum.

The above additions of thiazoles to methyl propiolate gave new and interesting ring systems which would probably be inaccessible by any other route.

It was disappointing to find that no pyrrolo[2,1-b] thiazole structures were observed or isolated. Addition of thiazole to two moles of propiolic ester might have formed the simple derivative (120) which could have been readily hydrolysed and decarboxylated to pyrrolo[2,1-b] thiazole, a much improved route over the existing formation of the triester (97) from the addition of thiazole to dimethyl acetylene-dicarboxylate (See page 57).



Section III deals with the hydrolysis and decarboxylation of the triester (97) and the subsequent preparation of 6-substituted derivatives. The attempted preparation of pyrrolo[2,1-b]thiazoles from the cyclisations of quaternary thiazolium salts is also discussed.

III. The Preparation of Pyrrolo[2,1-b]thiazoles

There has been little work reported on the synthesis of pyrrolo[2,1-b]thiazoles,[10,11,12] which are π-isoelectronic analogs of indolizine where the 7,8-bond has been replaced by a sulfur atom. Molloy[4] has prepared 6-substituted pyrrolo[2,1-b]thiazoles (See Introduction) but pyrrolo [2,1-b]thiazole itself was prepared in poor yield. It was

hoped that a better route to the parent compound would be found on addition of thiazoles to (1) dimethyl acetylene-dicarboxylate (Section I.) and (2) methyl propiolate (Section II.). The formation of the triester (97) from the addition of thiazole to dimethyl acetylenedicarboxylate has been realised (See Section II,D.) but hydrolysis and decarboxylation, described below, gave only traces of the parent compound.

[A] Decarboxylation studies of pyrrolo [2,1-b] thiazole-5,6,7-tricarboxylic acid.

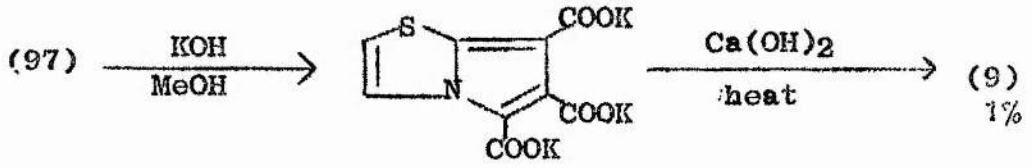
a) Thermal decarboxylation of the tripotassium salt.

The thermal decarboxylation of the readily accessible tripotassium salt of pyrrolo[2,1-b]thiazole-5,6,7-tricarboxylic acid (prepared by boiling a solution of the triester and potassium hydroxide under reflux in methanol) by heating with calcium hydroxide [83] gave an oil which could be converted to pyrrolo[2,1-b]thiazolium perchlorate (5 mg.) on addition of perchloric acid. The melting point was not depressed on admixture with an authentic sample.[4] The low yield prohibited any further characterisation of this compound.

Attempted decarboxylation of the tripotassium salt (121) using a mixture of (a) copper chromite/quinoline [84] and (b) copper chromite/triethanolamine [87] gave even

lower yields of product which could only be distinguished by a positive Ehrlich test.

The low yield of product obtained using calcium hydroxide and the unsuccessful attempts at isolating any product from the copper chromite decarboxylations were interpreted as being due to harsh reaction conditions. Any product formed was probably decomposed under the reaction temperatures.



(121)

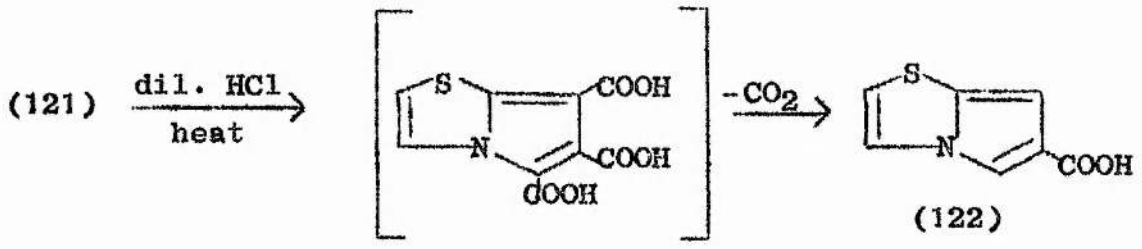
b) Preparation of pyrrolo[2,1-b]thiazole-6-carboxylic acid (122) and methyl ester (123)

It was decided to explore the conditions necessary for the hydrolysis and decarboxylation of trimethyl pyrrolo-[2,1-b]thiazole-5,6,7-tricarboxylate (97) to the 6-carboxylic acid (122) analogous to the preparation of indolizine-2-carboxylic acid (47) from hydrolysis and decarboxylation of the triester (45) (See Introduction pg. 19).

The 6-carboxylic acid (122) could be prepared in moderate yield (45%) by heating the tripotassium salt (121) with a mixture of concentrated hydrochloric acid and water

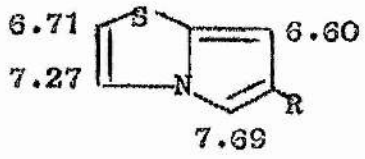
(1:3 v./v), the concentration of the acid solution was critical. Lower concentrations required a longer time before decarboxylation was complete and a subsequent loss of product through decomposition. Higher concentrations caused decomposition of the product concurrent with decarboxylation.

The best "work-up" procedure involved evaporation of the acid solution to dryness under vacuum and sublimation of the solid residue.



(122)

The 6-carboxylic acid (122) was characterised as its methyl ester (123), prepared by treating a solution of the acid in acetone with diazomethane. The proton magnetic resonance spectrum, in deuterochloroform (Plate 6) showed a group of signals (3H) at δ 3.81 (CO_2Me), two doublets of an AB system (2H) centred at δ 7.27 and 6.71 (J = 5.0 c./sec.), a singlet (1H) at δ 7.69 (J = 1.1 c./sec.) and a singlet (1H) at δ 6.60 (J = 1.1 c./sec.). The coupling constant of the thiazole ring protons agrees well with that of the corresponding protons in the triester (97) (J = 4.5 c./sec.).



(123)

The protons are not as deshielded due to the effect of only one ester group. The singlet at δ 7.69 is presumably the proton adjacent to nitrogen which exhibits allylic coupling with the C-7 proton (δ 6.60). The above data are given in support of structure (123) for the ester.

1) Attempted decarboxylation of pyrrolo[2,1-b] thiazole-6-carboxylic acid (122) using copper bronze

It was hoped that conditions might be found for smooth decarboxylation of the 6-carboxylic acid (122) to pyrrolo[2,1-b] thiazole. The problem involved finding not only the mildest decarboxylating conditions but also a method of isolating the product, from the reaction environment, as soon as it was formed.

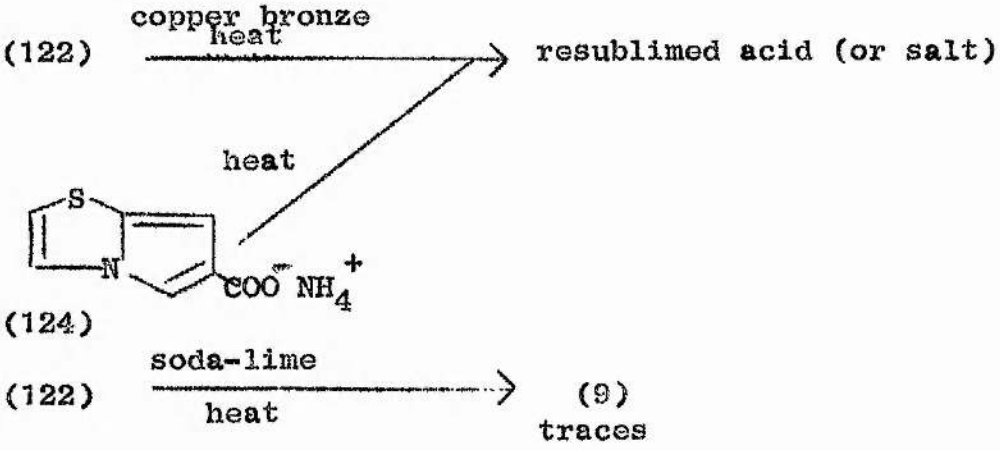
In this method, an intimate mixture of the 6-carboxylic acid (122) and copper bronze powder were heated at 300^{o} under water pump vacuum according to a method by Bullock, Gregory and Johnson.[85] Only resublimed acid was obtained.

2) Attempted decarboxylation of the ammonium salt (124) of pyrrolo[2,1-b] thiazole-6-carboxylic acid

A method used by Kermack, Perkin and Robinson [36] for the preparation of 6-methoxyindole by decarboxylation of the ammonium salt of the 2-carboxylic acid was applied to the 6-carboxylic acid (122). The dry ammonium salt (124) was heated at 200° under water pump vacuum and gave only the resublimed salt.

3) Attempted decarboxylation of pyrrolo[2,1-b] thiazole-6-carboxylic acid (122) with soda-lime

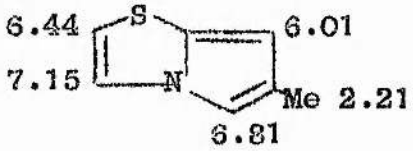
A method analogous to the formation of pyridine by decarboxylation of the 4,5,6-tricarboxylic acid over soda-lime [38] was applied to the decarboxylation of the 6-carboxylic acid (122). An intimate mixture of the 6-carboxylic acid (122) and excess soda-lime was heated at 200° under water pump vacuum. Traces of pyrrolo[2,1-b] thiazole were detected by Ehrlich's reagent but no perchlorate could be isolated.



4) Preparation of 6-methylpyrrolo[2,1-b]thiazole (125) from methyl pyrrolo[2,1-b]thiazole-6-carboxylate (123)

The 6-methyl ester (123) could be smoothly converted to the 6-methylpyrrolo[2,1-b]thiazole (125) by treatment with the lithium aluminium hydride/aluminium chloride complex [87] in 53% yield. The 6-methyl compound (125) was not stable on prolonged standing at room temperature. The melting point and infra-red spectrum were coincident with an authentic sample.[4]

The proton magnetic resonance spectrum, in deuterochloroform showed a singlet (3H) at δ 2.21 (CH_3) two characteristic doublets of an AB system (2H) centred at δ 7.15 and 6.44 (J = 4.5 c./sec.) a very broad band (1H) centred at δ 6.81 and a broad unresolved singlet (1H) at δ 6.01. The thiazole ring AB system has been assigned as in the 6-carboxylic



(125)

ester (123). The most interesting feature of this spectrum is the broad band around δ 6.81, indicating slow change of the proton adjacent to nitrogen. This is interpreted as

being due to traces of DCl in the deuterochloroform which are catalysing slow exchange of this proton. Similar effects have been observed in the spectra of other pyrrolo[2,1-b] thiazoles by other workers in this laboratory. The singlet (δ 6.01) is assigned to the C-7 proton but its coupling with the C-6 methyl group is unresolved. These facts are in accord with the structure (125).

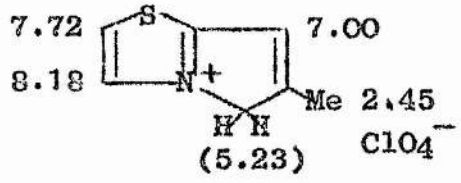
The above values agree well with those determined from a spectrum of the compound in carbon tetrachloride, except that the C-5 proton is well resolved in the latter spectrum.[4]

i) Protonation

6-Methylpyrrolo[2,1-b] thiazolium perchlorate (126) was prepared by the addition of excess perchloric acid (70%) to a solution of the 6-methyl compound (125) in ethanol. The recrystallised perchlorate (m.pt. 121-123.0°) was dried in vacuo.

The proton magnetic resonance spectrum of the perchlorate (126) in trifluoroacetic acid showed the signals of a doublet (3H) at δ 2.42 (CH_3)(J = 1.6 c./sec.) a broad singlet (1H) at δ 6.98 (J = 1.6 c./sec.), a singlet (2H) at δ 5.24 (CH_2) and an AB system (2H) centred at δ 7.69 and 8.20.

These values agree well with those found by Molloy [4] for the spectrum of the same compound in trifluoroacetic acid, showing that protonation does indeed occur at the C-5 position. See compound (126) below.



(126)

[B] Cyclisation reactions of quaternary thiazolium salts in aprotic solvents

It was decided to extend the work on the cyclisations of quaternary thiazolium salts, investigated by Molloy [4,12] (See Introduction).

a) The preparation of 3-acetonyl-2,4-dimethylthiazolium perchlorate, 3-acetonyl-2-methylthiazolium perchlorate and 2-methyl-3-phenacylthiazolium bromide

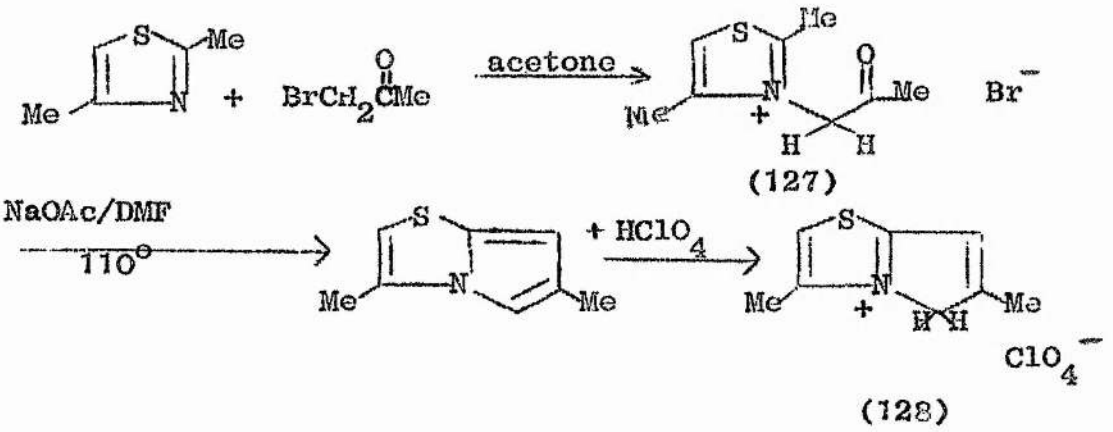
These quaternary thiazolium salts were prepared by the reaction of the respective thiazoles with either bromoacetone or phenacyl bromide, according to the method of Molloy, Reid and Skelton.[12]

Both bromoacetone and phenacyl bromide could be prepared in good yield by the methods of Levene,[88] and Cowper and Davidson,[89] respectively.

3-Acetonyl-2,4-dimethylthiazolium perchlorate, m.pt. 172 - 186.0° (not previously described) was prepared by treatment of the bromide with an excess of perchloric acid.

b) Cyclisation using aprotic solvents

The cyclisation of 3-acetonyl-2,4-dimethylthiazolium perchlorate (127) was attempted in various aprotic solvents under an atmosphere of nitrogen in an effort to increase the yield of the respective pyrrolo[2,1-b] thiazoles (Table 6). The results demonstrate that alkali - metal acetates give low yields of pyrrolo[2,1-b] thiazoles directly without having to isolate the intermediate acetyl compounds. The best yield (8%), isolated as 3,6-dimethyl-5H- pyrrolo[2,1-b] thiazolium perchlorate (128), was obtained by cyclisation with sodium acetate in dimethylformamide.



Cyclisation of 2-methyl-3-phenacylthiazolium bromide and of 3-acetonyl-2-methylthiazolium perchlorate, under the same conditions, gave 6-phenylpyrrolo[2,1-b] thiazole (5.2%) and 6-methylpyrrolo[2,1-b] thiazole, isolated as the perchlorate (1%).

[C] Attempted cyclisation of quaternary thiazolium salts using other methods.

a) Attempted cyclisation of 3-acetonyl-2-methylthiazolium perchlorate (129) using thionyl chloride.

A method of cyclisation employed by Thurman using thionyl chloride has recently appeared in the literature.[90] It was decided to apply this reagent to the cyclisation of 3-acetonyl-2-methylthiazolium perchlorate (129). The small residue obtained after "work-up" of the reaction mixture gave a negative Ehrlich test.

b) Attempted cyclisation of 3-formylmethyl-2-methylthiazolium chloride (130) using sodium acetate and acetic anhydride.

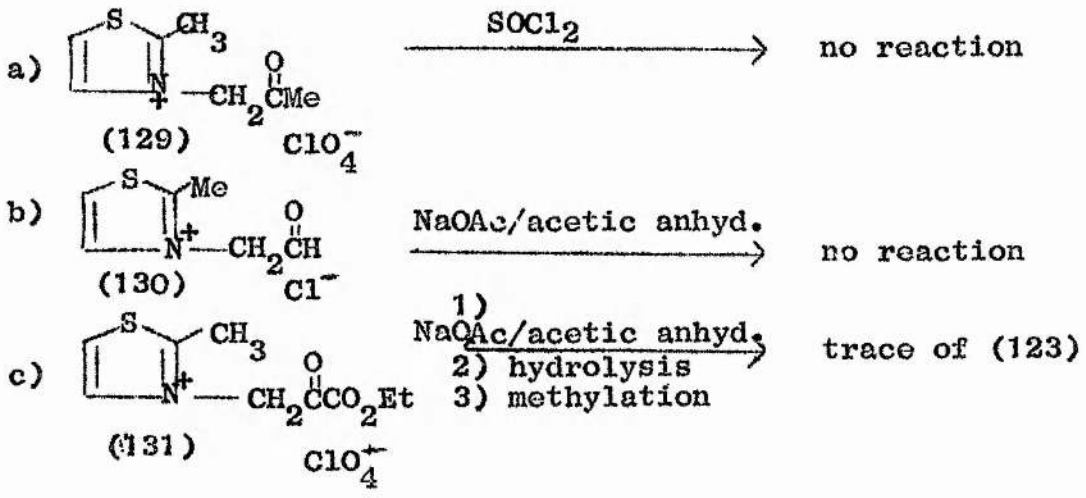
It was hoped that 3-formylmethyl-2-methylthiazolium chloride (130) could be cyclised to the parent pyrrolo[2,1-b]thiazole using the sodium acetate/acetic anhydride conditions but Ehrlich's test of the residue from the reaction mixture was again negative. It is suspected that either (1) the reaction of chloroacetaldehyde hydrate and 2-methylthiazole did not form the expected quaternary thiazolium salt or (2) hydrolysis of the acetylated derivative caused decomposition of any pyrrolo[2,1-b]thiazole formed. The lack of even a trace of product (evidenced by a negative Ehrlich test) indicates that the quaternary thiazolium salt

was probably not formed.

c) Attempted cyclisation of the quaternary salt (131) using sodium acetate and acetic anhydride.

Finally the preparation of pyrrolo[2,1-b]thiazole-6-carboxylic acid was attempted by the reaction of ethyl bromopyruvate [91] with 2-methylthiazole and subsequent cyclisation of the quaternary thiazolium salt (131) using sodium acetate and acetic anhydride. The solid material isolated after hydrolysis of the acetylated material gave a mixture of esters on treatment with diazomethane. Thin-layer chromatography showed only a trace of material coincident with an authentic sample of methyl pyrrolo[2,1-b]thiazole-6-carboxylate (123) prepared by hydrolysis and decarboxylation of the triester (97). Molloy also obtained a mixture of products from the reaction of 2,4-dimethylthiazole with ethyl bromopyruvate and subsequent cyclisation using sodium bicarbonate.[4]

These attempted cyclisations are given below.



IV Miscellaneous Reactions

[A] The addition of 2-methylthiazoline to dimethyl acetylenedicarboxylate

It was decided to investigate the structure of the products from the addition of 2-methylthiazoline to dimethyl acetylenedicarboxylate in an effort to gain further information on the structures of the corresponding thiazole adducts.

a) Preparation of 2-methylthiazoline

2-Methylthiazoline was prepared from N-acetyl-2-ethanolamine, according to the method of Wenker [92] and the purity of the product was checked by gas-liquid chromatography.

b) Preparation of the adducts

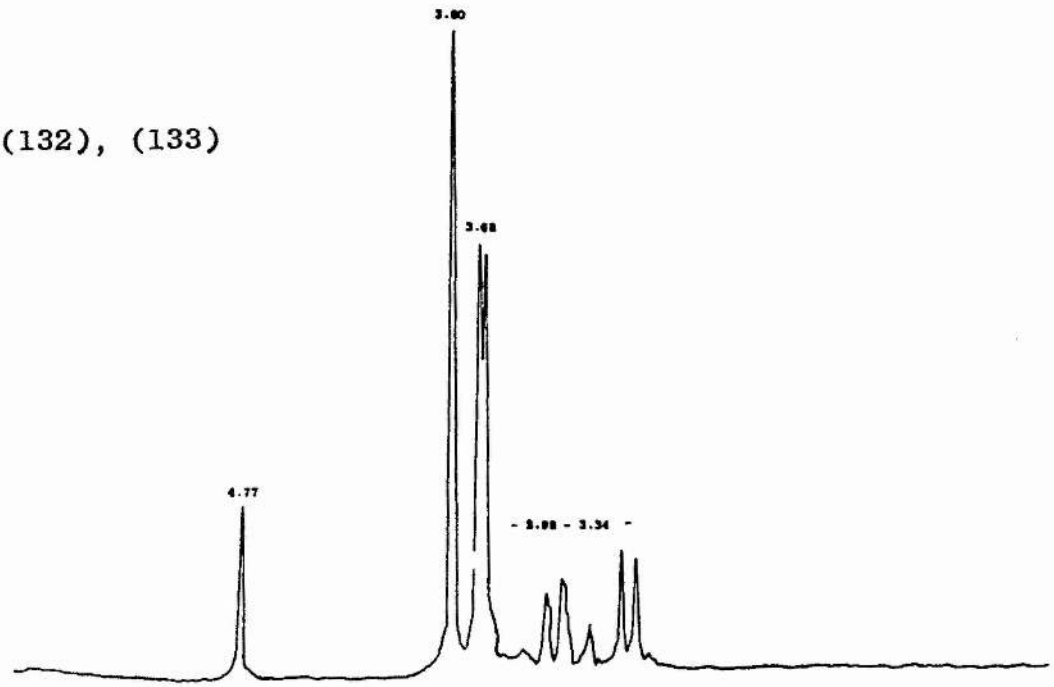
The addition of 2-methylthiazoline (1 mmole) to dimethyl acetylenedicarboxylate (2 mmole) gave the same two products in dimethylformamide, ether and acetonitrile. Ether deposited a mixture of both adducts which could be separated by chromatography. Analytical data showed that one molecule of the 2-methylthiazoline had combined with two molecules of the ester in both adducts.

1) Proton magnetic resonance spectra

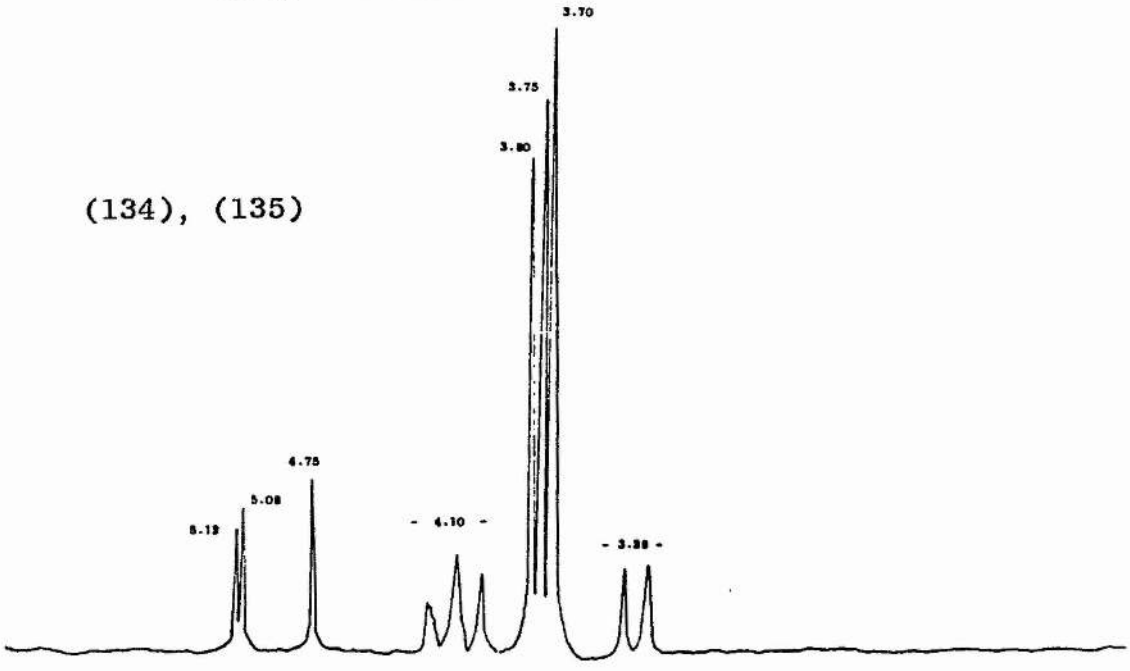
The proton magnetic resonance spectrum of the less polar product, in deuterochloroform, showed a group of signals (12H) at δ 3.68 and 3.80 ($4CO_2Me$), a group of multiplets (4H) at δ 2.92 - 3.58 ($2CH_2$) and a sharp

PLATE 9.

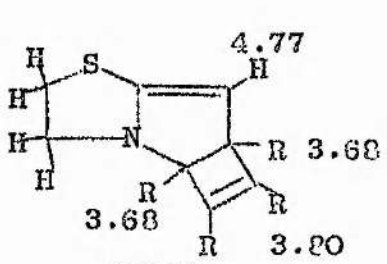
(132), (133)



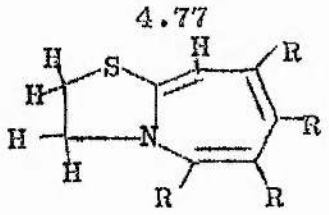
(134), (135)



singlet (1H) at δ 4.77. The ester complex is split into two sharp singlets (one of which is slightly split) each equivalent to (6H) and may indicate one pair of ester groups on tetrahedral carbon atoms and the other on unsaturated carbon atoms. The multiplet (δ 2.98 - 3.34) is in the correct region of the spectrum to be assigned to the C-4 and C-5 methylene protons of the thiazoline residue. The singlet (δ 4.77) is unsplit and must be a vinylic proton derived from the C-2 methyl group of the 2-methylthiazoline. These data suggest structures (132) or (133) for the product.



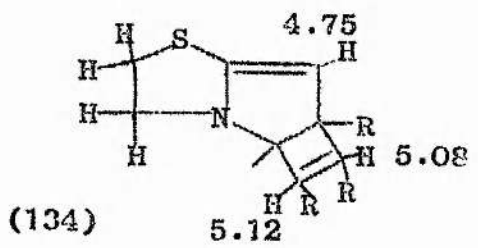
(132)



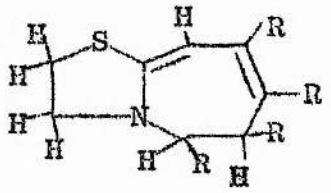
(133)

The proton magnetic resonance spectrum of the more polar product, in deuterochloroform, showed a group of signals (12H) at δ 3.70, 3.75 and 3.80($4CO_2Me$), two poorly resolved doublets (4H) centred at δ 3.28 and 4.10 and three singlets (3H) at δ 4.75, 5.08 and 5.12. The poorly resolved doublets have been assigned to the methylene protons of the thiazoline residue and the singlet (δ 4.75) to the vinylic proton from the C-2 methyl group of 2-methylthiazoline. The protons (δ 5.08 and 5.12) could be assigned to a pair of adjacent protons on tetrahedral carbon atoms of a

4 membered ring. The conformation of the structure may be such as to prevent appreciable coupling between these protons.[93,94] Therefore, the characteristic AB pattern has been reduced to two singlets. Examples of anomalous coupling between protons has been found to occur in cyclobutane structures.[95] This interpretation of the data suggests structure (134) for the compound.



(134)



(135)

The conformation of the structure (135), analogous to the 5,6-dihydrothiazolo [3,2-a] azepines in the thiazole series, may be responsible for the near equivalence of the protons of the 7-membered ring AB system and this structure must also be considered.

2) Infra-red and ultraviolet spectra

The infra-red spectra (Table 5) of both products showed bands typical of ester functions in the 5-7 mμ region of the spectrum.

The ultraviolet absorption spectrum (Table 4), in methanol, of the least polar product showed three maxima at 211 mμ, 273 mμ and 428 mμ, surprisingly similar to the spectrum of the [5,2,0]-bicyclic structures. Unfortunately,

there was not enough material to obtain the ultraviolet absorption spectrum of the more polar product.

No further investigations of these structures were conducted. It was intended to attempt the Raney nickel desulfurisation of the more polar product. If structure (135) is correct then an azepine of similar structure to the azepine (91), prepared from a similar desulfurisation of the structure (87), should be obtained. There was no time to carry out this investigation.

It might also be interesting to study the addition of thiazolines to dimethyl acetylenedicarboxylate in a variety of solvents in order to determine whether 2,3-dihydropyrrolo-[2,1-b] thiazoles are formed.

[B] The addition of benzothiazole to dimethyl acetylenedicarboxylate in methanol and acetonitrile.

It was hoped that a benzopyrrolo[2,1-b] thiazole triester, analogous to the triester (97), would be formed on addition of benzothiazole to dimethyl acetylenedicarboxylate.

The addition of benzothiazole (1 mmole) to dimethyl acetylenedicarboxylate (2 mmole) in dimethylformamide, ether, methanol and acetonitrile showed only appreciable reaction in methanol and acetonitrile. Both solvents gave low yields of both a yellow and a white product.

a) Proton magnetic resonance spectrum

Interest was directed to the white product (136) since

it gave an Ehrlich test on prolonged boiling with concentrated hydrochloric acid, indicative of a pyrrole ring.

The proton magnetic resonance spectrum of the white product in deuterochloroform showed a group of signals (6H) at δ 3.70 and 3.74 ($2CO_2Me$), two doublets (2H) at δ 4.51 and 6.14 (J = 3.6 c./sec.), a sharp singlet (4H) at δ 7.19 and a sharp singlet (1H) at δ 8.78.

Initial inspection of the spectrum shows that the product does not possess a benzopyrrolo[2,1-b] thiazole structure. The position of the signals (δ 3.70 and 3.74) indicates the corresponding protons of two ester groups. The signal (δ 7.19) is assigned to the four aromatic protons. The signals at δ 4.51, 6.14 and 8.78 have not been assigned.

It is difficult to visualise a structure that will accommodate the number of protons indicated by the proton magnetic resonance data and a structure is not being offered.

b) Infra-red and ultraviolet spectra

Characteristic bands in the 5-7 mμ region of the infra-red spectrum were obtained for the white product.

The ultraviolet absorption spectrum showed three maxima at 227 mμ, 254 mμ and 310 mμ (See Table 4).

The proton magnetic resonance spectrum of the yellow product (137) was not done but the ultraviolet absorption spectrum showed four maxima, in contrast to the white

product, at 216 mμ, 270 mμ, 294 mμ and 424 mμ. These maxima are in agreement with those found by Acheson [67] for structure (133) isolated from the reaction of benzothiazole with dimethyl acetylenedicarboxylate at 0° without solvent. Even though the ultraviolet spectral data are in agreement with Acheson's product, we believe that our yellow product is of a different structure since the analytical data, melting point and lack of solubility in non-polar solvents do not agree with his data.

Further investigations of the structures of these adducts were not made.

[C] The white isomers from the addition of 2-ethylthiazole and 2-ethyl-4-methylthiazole to dimethyl acetylenedicarboxylate in dimethylformamide.

a) Proton magnetic resonance spectra

It was hoped that the proton magnetic resonance spectra of the white isomers (60) and (65) (these numbers do not refer to formulae) would be decisive in the elucidation of their structure but some signals could not be assigned.

The proton magnetic resonance spectrum of the compound (160) in deuterochloroform showed a group of signals (12H) at δ 3.67 - δ 3.77 ($4CO_2Me$), a doublet (3H) at δ 1.28(CH_3) (J = 6.7 c./sec.) , a doublet (1H) centred at δ 3.02 (J = 10.3 c./sec.) a weakly split singlet (3H) at δ 2.19

(J = 1.2 c./sec.) and a broad singlet (1H) at δ 5.79 (J = 1.2 c./sec.). The singlet (δ 2.19) has been assigned to the protons of what was the 4-methyl group of 2-ethyl-4-methylthiazole which are slightly coupled to the proton (δ 5.79) on what was the C-5 position. The signals of both doublets have not been assigned and no structure is proposed for this adduct.

The proton magnetic resonance spectrum of the compound (65), in deuterochloroform, was very similar to that of compound (60) and showed a group of signals (12H) at δ 3.67 - δ 3.79 ($4CO_2Me$), a doublet (2H) centred at δ 1.30 (CH_3) (J = 6.5 c./sec.) a doublet (1H) at δ 3.04 (J = 10.2 c./sec.) and two doublets (2H) of an AB system centred at δ 6.17 and 6.99 (J = 4.5 c./sec.). The signals of the AB system can be assigned to the thiazole ring protons at C-4 and C-5 but those of both doublets have not been assigned and no structure can be proposed.

b) Infra-red and ultraviolet spectra

The infra-red spectra of both compounds showed a greater number of bands than were found in the corresponding spectra of their isomeric structures (63) and (74). More bands in the 5-7 μ region were also visible. This may indicate that the white isomers have less symmetric structures. No acetylenic stretching vibrations at 2200 cm^{-1} were observed and structures similar to structure (40), isolated by Acheson [49], could not be considered.

The ultraviolet absorption spectra showed only one maximum around 345 mμ.

Both isomers were found to be quite stable on being boiled with conc. hydrochloric acid but neither gave a positive Ehrlich test. They could also be heated well above their melting point before decomposition took place. It seems quite clear that the structures do not clearly correspond to any that have yet been isolated in this series.

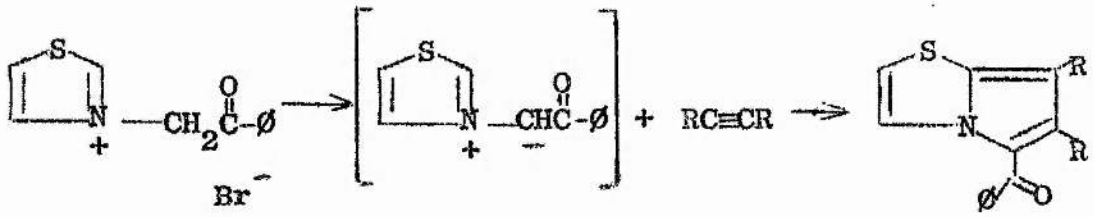
[D] Reaction of phenacylthiazolium bromide with dimethyl acetylendicarboxylate

a) Preparation of phenacylthiazolium bromide

Phenacylthiazolium bromide was prepared by boiling a mixture of thiazole and phenacyl bromide under reflux in acetone.

b) Preparation of the adduct

A dipolar addition of phenacylthiazolium bromide (139) to dimethyl acetylenedicarboxylate was attempted in order to see if the addition would lead to a pyrrolo[2,1-b] thiazole structure of the type (141) shown below.



(139) (140) (141)

The yellow product that was isolated gave a negative Ehrlich test and was not reversibly protonated by strong mineral acid. When the reaction was carried out under nitrogen, in order to prevent any undesirable side reactions of the active zwitterion (140), the yield of product was improved.

1) Proton magnetic resonance spectrum

The proton magnetic resonance spectrum of the product, in deuterochloroform, showed a sharp singlet (3H) at δ 3.28 (CO_2Me), two sharp singlets (6H) at δ 3.82 and 3.90 ($2CO_2Me$), two doublets of an AB system (2H) centred at δ 6.42 and 7.24 (J = 3.5 c./sec.) a sharp singlet (1H) at δ 6.88 and a complex band of multiplets (10H) at δ 7.42 - 7.98.

It was difficult to interpret this spectrum other than the fact that a pyrrolo[2,1-b]thiazole structure was not indicated and no further investigations of the structure of this product were carried out.

[E] Attempted reactions of a)ditetrahydropyranyl acetylenedicarboxylate with (1) 2-methylthiazole and (2) phenacylpyridinium bromide and b) acetylene with 2-methylthiazole.

a) It was decided to study the reaction of ditetrahydropyranyl acetylenedicarboxylate with thiazoles in an attempt to prepare the adducts corresponding to

those isolated from the reactions of thiazoles with dimethyl acetylenedicarboxylate. Ready hydrolysis of the tetrahydropyranyl ester groups might be a simple route to the parent acids, if stable enough to be isolated. As an example, the ester groups of the tritetrahydropyranyl ester corresponding to the triester (97) could be easily hydrolysed using mild conditions and a good yield of the pyrrolo[2,1-b]thiazole tricarboxylic acid might be obtained.

The preparation of ditetrahydropyranyl acetylenedicarboxylate was attempted from 2,3-dihydropyran and acetylene dicarboxylic acid according to a method by Johnson, Christiansen and Ireland.[96] A crude product was isolated on removal of the solvent at 40°.

It was surprising to find that the reactions of 1) 2-methylthiazole (1 mmole) and 2) phenacylpyridinium bromide[97] (1 mmole), with the crude ester (2 mmole) in (1) ether, (2) dimethylformamide, (3) methanol and (4) acetonitrile were both unsuccessful at room temperature.

The reasons for this are not clear but it is suspected that the crude ester was not the expected ditetrahydropyranyl acetylenedicarboxylate. The acetylene dicarboxylic acid might be a strong enough acid to prevent the formation and isolation of this ester.

(b) 2-Methylthiazole (1 mmole) was added to a solution of dry N-methyl-2-pyrrolidone saturated with dry acetylene and the reaction mixture was allowed to stand under ultraviolet

light for 24 hours. No evidence of reaction was observed at the end of this time and thin-layer chromatography showed only the presence of the reactants.

Evidently the triple bond is not activated enough for nucleophilic attack by the nitrogen atom of the thiazole.

SECTION C

EXPERIMENTAL

Introduction

All melting points were determined on a Kofler heating block apparatus and are corrected as listed.

Elemental analyses were done by Drs. Weiler and Strauss, Oxford, England and A. Bernhardt, Max-Planck Institute, Mülheim, Germany.

Mass spectra were recorded by W. Bonthrone, Milstead Laboratory of Chemical Enzymology, Sittingbourne, Kent.

Proton magnetic resonance spectra were recorded on a Perkin Elmer model R10, 60 mc., instrument.

Infra-red spectra were recorded on a Grubb-Parsons Model G.S. 2A instrument and a Perkin Elmer Model 137 infracord spectrophotometer.

Ultraviolet and visible spectra were recorded on a Unicam S.P. 600 spectrophotometer. Light absorption data refer to methanol solutions unless otherwise specified. Abbreviations are B = broad, S = shoulder.

Thin-layer chromatography was carried out by the method according to Stahl using Desaga equipment. Compounds were spotted on "Silica gel G" plates, eluted with ether and developed in iodine vapour unless otherwise stated.

All column chromatography was done with activated Spence "H" alumina unless otherwise specified.

Gas liquid chromatography was carried out on a Perkin Elmer 451 Fractometer fitted with a flame ionization detector. Separations were usually carried out on an "Autoprep A-700" automatic preparative gas chromatograph.

Thiazoles and 2-methylthiazoline were individually checked for purity by running a sample on the Perkin Elmer 451 gas-liquid Fractometer, utilizing a one meter 20% polyethylene glycol succinate column at a temperature of 110°. All samples were found to be > 99% pure product except for 2,4,5-trimethylthiazole, which contained 20% impurity. This was removed by chromatography of a sample (5 gm.) through a column (55 cm. x 3 cm.) of Spence's, "Type H", alumina eluting with dry ether.

Acetonitrile, chloroform, dioxan and methylene chloride were distilled from phosphorus pentoxide and redistilled through a Vigreux column (50 cm.) before use.

Acetone was dried over calcium chloride for 48 hours and distilled through a Vigreux column (50 cm.).

Benzene was dried over calcium chloride for 48 hours, boiled under reflux with sodium wire for 0.5 hours and distilled.

Diethyl ether was dried over calcium chloride for 48 hours and distilled over lithium aluminium hydride.

N,N' dimethylformamide (DMF) was dried by allowing it to stand over potassium hydroxide pellets for 48 hours and then distilled under reduced pressure.

Dimethyl sulfoxide was dried over calcium hydride and distilled under reduced pressure.

Ethanol was redistilled commercial absolute ethanol.

Methanol was dried according to the method of Vogel utilizing magnesium methylate and distilled through a Vigreux column (50 cm.).

Petroleum ether, normally referred to as hexane, was the redistilled fraction boiling at 40-60.0°.

Acetic anhydride was fractionally distilled and the fraction boiling at 140.0° was collected.

Acetic acid was of "AnalaR" grade.

Perchloric acid refers to 70-72% "AnalaR" grade, unless otherwise specified.

Pyridine was dried over potassium hydroxide pellets and distilled through a Vigreux column (50 cm.).

I. Reactions of Dimethyl Acetylenedicarboxylate with Thiazoles

A. Preparation of Thiazoles and Dimethyl Acetylenedicarboxylate

(a) Thiazole was prepared according to the method of Popp.[59]

(b) 2-Methylthiazole was prepared according to the method of Hantzsch.[60]

(c) 4-Methylthiazole was prepared according to the method of Popp.[61]

(d) 2-Ethylthiazole was prepared according to the method of Erlenmeyer, Weber, Schmidt, Küng, Zinsstag and Prijs.[62]

(e) 2-t-Butylthiazole

A mixture of redistilled chloroacetal (15 gm., 100 mmoles) and anhydrous oxalic acid (9.5 gm., 100 mmoles) was heated under reflux at 140° for 4 hours. The mixture was cooled in an ice bath and thiopivalamide (11 gm., 100 mmoles) was added all at once. The mixture was then boiled for 1 hr. on a water bath. A mixture of water (10 ml.) and conc. hydrochloric acid (10 ml.) was added. The mixture was then boiled for a further hour on the water bath. The mixture was filtered through glass wool and basified with caustic soda until strongly alkaline.

The mixture was steam distilled and about 500 ml. of distillate was collected and acidified with conc. hydrochloric acid. The acid solution was concentrated to one third its volume, basified with alkali and saturated with potassium carbonate. The solution was extracted thrice with 150 ml. portions of ether. The extracts were combined, dried (potassium carbonate) and evaporated. Distillation of the crude oil gave 2-t-butylthiazole (6.0 gm., 48%), B.pt. 158.0 - 160.0°, 55.0°/10 mm. (lit. 75.0°/ 46 mm.)[102]

Found C = 59.92, H = 7.82

$C_7H_{11}NS$ requires C = 59.60, H = 7.80%

(f) 2,4-Dimethylthiazole was prepared according to the method of Kurkjy and Brown.[64]

(g) 2,5-Dimethylthiazole was prepared according to the method used for the preparation of 2,4-dimethylthiazole (I,A,f.).

(h) 2-Ethyl-4-methylthiazole was prepared according to the method used for the preparation of 2,4-dimethylthiazole (I,A,f).

(i) 2,4,5-Trimethylthiazole was prepared according to the method used for the preparation of 2,4-dimethylthiazole (I,A,f).

(j) Benzothiazole and 2-methyl benzothiazole were both purchased from L. Light and Company Ltd., Bucks, England and redistilled before use.

(k) Dimethyl acetylenedicarboxylate was prepared according to the method of Huntress, Lesslie and Bornstein.[65]

B. The addition of thiazoles to dimethyl acetylenedicarboxylate in dimethylformamide.

(a) Preparation of the [3,4,0]-bicyclic structures (8aH-thiazolo[3,2-a]pyridines)

1) 2-Ethyl-4-methylthiazole (2.54 gm., 20 mmole) was dissolved in dimethylformamide (25 ml.) and dimethyl acetylenedicarboxylate (5.68 gm., 40 mmole) was added slowly with stirring at room temperature. The reaction was allowed to proceed with occasional stirring, at room temperature, for 96 hr. At the end of this time, any solid adduct was removed by filtration and the solvent was removed under water pump vacuum (13 mm.). The residue was dissolved in the minimum amount of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. The column was eluted with a mixture of methylene chloride (500 ml.) and ether (500 ml.) and 10,100 ml., fractions were collected. The fractions were checked for homogenity by thin-layer chromatography and combined where possible before being evaporated. The latter fractions contained a colourless adduct and the former, a red adduct. After evaporation of solvent, both adducts could be readily crystallised by light trituration with methanol. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave (i) tetramethyl 3-methyl-8a-ethyl-8aH-thiazolo[3,2-a] pyridine-5,6,7,8-tetracarboxylate (63), (2.50 gm., 31%), as orange red prisms, m.pt. 122-125°.

Found C = 52.77, H = 5.06, N = 3.22, S = 7.60

$C_{18}H_{21}NO_8S$ requires C = 52.55, H = 5.15, N = 3.40, S = 7.78%.

and (ii) white prisms of an isomer (60) (200 mg., 2%) m.pt. 199.0-200.0°.

Found C = 52.37, H = 4.95, N = 3.36, S = 7.90

$C_{18}H_{21}NO_8S$ requires C = 52.55, H = 5.15, N = 3.40, S = 7.78%.

The yield of products did not change when the above reaction was carried out under an atmosphere of nitrogen.

T.L.C. showed the same products when the reactants were mixed and allowed to react at 0°.

No reaction was observed at -60°.

Similarly:

2) 2,4-dimethylthiazole(2.26 gm.,20 mmole) gave tetramethyl 3,8a-dimethyl-8aH-thiazolo[3,2-a]pyridine-5,6,7,8-tetracarboxylate (61), (2.80 gm., 37%), as orange red rods, m.pt. 145.5 - 147.0°., mol.wt. (mass spectrum) 397.

Found C = 51.78, H = 4.72, N = 3.36, S = 7.72

$C_{17}H_{19}NO_8S$ requires C = 51.40, H = 4.78, N = 3.53, S = 8.08%.

3) 2,4,5-trimethylthiazole (2.54 gm., 20 mmole) gave tetramethyl 2,3,8a-trimethyl-8aH-thiazolo[3,2-a]pyridine-5,6,7,8-tetracarboxylate (64), (2.40 gm., 30%), as red prisms, m.pt. 159.5 - 161.5°.

Found C = 52.53, H = 5.38

$C_{18}H_{21}NO_8S$ requires C = 52.54, H = 5.15%.

(b) Preparation of the [5,2,0]-bicyclic structures (8aH-azeto[1,2-d][1,4]thiazepines or 1,4-thiazonines).

1) 2-Ethylthiazole (2.26 gm., 20 mmoles) was dissolved in dimethylformamide (25 ml.) and dimethyl acetylenedicarboxylate (5.68 gm., 40 mmole) was added slowly with stirring at room temperature. The reaction was allowed to proceed with occasional stirring for 96 hr. At the end of this time, any solid adduct was removed by filtration and the solvent was removed under water pump vacuum (13 mm.). The residue was dissolved in the minimum amount of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. The column was eluted with a mixture of methylene chloride (500 ml.) and ether (500 ml.) and 10,100 ml., fractions were collected. The fractions were checked for homogenity by thin-layer chromatography and combined, where possible, before being evaporated. The latter fractions contained a colorless adduct and the former, a red adduct. After evaporation of solvent, both adducts could be readily crystallised by light trituration with methanol. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave (i) tetramethyl-2-ethyl-8aH-azeto[1,2-d][1,4]thiazepine-1,7,8,8a-tetracarboxylate (74), (2.70 gm., 34%), as orange red prisms, m.pt. 162.5 - 164.5°.

Found C = 51.47, H = 4.85, N = 3.81, S = 8.21

$C_{17}H_{19}NO_8S$ requires C = 51.40, H = 4.78, N = 3.53, S = 8.08%.

and (ii) white prisms of an isomer (850 mg., 11%),(65), m.pt. 160.5 - 162.5°.

Found C = 51.07, H = 4.81

$C_{17}H_{19}NO_8S$ requires C = 51.40, H = 4.78%.

The yield of products did not change when the above reaction was carried out under an atmosphere of nitrogen.

No reaction was observed at -60°.

Similarly:

2) Thiazole (1.70 gm., 20 mmole) gave tetramethyl 8aH-azeto[1,2-d][1,4]thiazepine-1,7,8,8a-tetracarboxylate (66), (1.34 gm.,20%), as orange prisms, m.pt. 147.0 - 149.0°.

Found C = 48.80, H = 4.15, N = 4.04, S = 8.97

$C_{15}H_{15}NO_8S$ requires C = 48.82, H = 4.06, N = 3.79, S = 8.67%

3) 4-Methylthiazole (1.98 gm., 20 mmole) gave tetramethyl 5-methyl-8aH-azeto[1,2-d][1,4]thiazepine-1,7,8,8a-tetracarboxylate (71), (3.30 gm., 43%), as orange tablets, m.pt. 221 - 223.0°, mol.wt. (mass spectrum) 383.

Found C = 50.31, H = 4.58, N = 3.83

$C_{16}H_{17}NO_8S$ requires C = 50.12, H = 4.47, N = 3.65%.

4) 2-Methylthiazole(1.98 gm., 20 mmole) gave tetramethyl 2-methyl-8aH-azeto.1,2-d][1,4]thiazepine-1,7,8,8a-tetracarboxylate (72), (2.50 gm., 36%), as orange prisms, m.pt. 159.5 - 161.0°.

Found C = 49.76, H = 4.46, N = 3.78, S = 8.51

$C_{16}H_{17}NO_8S$ requires C = 50.12, H = 4.47, N = 3.65, S = 8.36%

5) Attempted addition of 2-t-butylthiazole to dimethyl acetylenedicarboxylate in dimethylformamide

A mixture of 2-t-butylthiazole (141 mg., 1 mmole), dimethylformamide (2 ml.) and dimethyl acetylenedicarboxylate (284 mg., 2 mmole) was subjected to the following conditions: (1) allowed to remain at room temperature for 96 hrs., (2) heated at 100° on a boiling water bath for 6 hrs., (3) boiled under reflux for 6 hrs.

Reactions 1 and 2 gave no products as shown by thin-layer chromatography. Reaction 3 produced some non-polar material but not in isolable amount. All three reactions gave substantial amounts of intractable tars, evidenced by thin-layer chromatography. The reaction was not further investigated.

6) 2,5-Dimethylthiazole (2.26 g., 20 mmole) gave tetramethyl 2,7-dimethyl-8aH-azeto[1,2-d][1,4]thiazepine - 1,7,8,8a-tetracarboxylate (73), (2.90 gm., 36%), as orange prisms, m.pt. 177.5 - 179.5°.

Found C = 51.36, H = 4.86

$C_{17}H_{19}NO_8S$ requires C = 51.38, H = 4.79%

C. The addition of 2-alkylthiazoles to dimethyl acetylene-dicarboxylate in methanol or acetonitrile.

(a) Preparation of the [3,5,0]-bicyclic structures, 5,6-dihydrothiazolo[3,2-a]azepines

1) 2-Ethylthiazole (2.26 gm., 20 mmole) was dissolved in acetonitrile (25 ml.) and dimethyl acetylene-

dicarboxylate (5.68 gm., 40 mmole) was added slowly with stirring at room temperature. The reaction was allowed to proceed with occasional stirring, at room temperature, for 96 hrs. At the end of this time, the solvent was removed under water pump vacuum (13 mm.). The residue was dissolved in the minimum amount of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. The column was eluted with ether (1 litre) or until all of the yellow material was removed. After evaporation of solvent, the yellow adduct crystallised on trituration with methanol. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave tetramethyl 5,6-dihydro-9-methylthiazolo[3,2-a]azepine-5,6,7,8-tetracarboxylate (87), (820 mg., 10%), as yellow prisms, m.pt. 206 - 208.0°.

Found C = 51.28, H = 4.57, N = 3.90, S = 8.31

$C_{17}H_{19}NO_8S$ requires C = 51.50, H = 4.78, N = 3.53, S = 8.08%

Thin-layer chromatography showed the same products when the reactants were mixed and allowed to react at 0°.

The yield of product was the same when the reaction was carried out under an atmosphere of nitrogen.

Similarly:

2) 2-Methylthiazole (1.98 gm., 20 mmole) gave tetramethyl 5,6-dihydrothiazolo[3,2-a]azepine-5,6,7,8-tetracarboxylate (85), (100 mg., 1.3 %), as yellow prisms, m.pt. 172.5 - 175.5°.

Found C = 50.15, H = 4.61, N = 3.83, S = 8.54

$C_{16}H_{17}NO_8S$ requires C = 50.12, H = 4.47, N = 3.65, S = 8.36%.

3) 2,4-Dimethylthiazole (2.26 gm., 20 mmole) gave tetramethyl 5,6-dihydro-3-methylthiazolo[3,2-a]azepine-5,6,7,8-tetracarboxylate (88), (1.20 gm., 15%), as yellow prisms, m.pt. 154.0 - 156.0°.

Found C = 51.75, H = 4.86, N = 3.46, S = 8.08

$C_{17}H_{19}NO_8S$ requires C = 51.40, H = 4.78, N = 3.53, S = 8.08%.

4) 2-Methylbenzothiazole (2.98 gm., 20 mmole) gave tetramethyl 5,6-dihydrobenzothiazolo[3,2-a]azepine-5,6,7,8-tetracarboxylate (89), (6.30 gm., 73%), as yellow prisms, m.pt. 201.0 - 211.0°.

Found C = 55.27, H = 4.32, N = 3.51, S = 7.23

$C_{20}H_{19}NO_8S$ requires C = 55.40, H = 4.39, N = 3.23, S = 7.39%.

D. The addition of thiazole to dimethyl acetylenedicarboxylate in methanol

(a) Preparation of trimethyl pyrrolo[2,1-b]thiazole-5,6,7-tricarboxylate.

Thiazole (1.70 gm., 20 mmole) was dissolved in methanol (25 ml.) and dimethyl acetylenedicarboxylate (5.68 gm., 40 mmole) was added slowly with stirring at room temperature. The reaction mixture was set aside with occasional stirring for 10 days. The solid product was filtered and the reaction allowed to proceed for another

4 days or until no more solid product was formed (larger reactions required a longer period of time). Recrystallisation twice, from a mixture of methylene chloride and methanol (1:1) gave trimethyl pyrrolo[2,1-b]thiazole-5,6,7-tricarboxylate (97), (800 mg., 8.5 %), as colorless prisms, m.pt. 154.0 - 157.0°.

Found C = 55.27, H = 4.32, N = 3.51, S = 7.23

$C_{12}H_{11}NO_6S$ requires C = 55.40, H = 4.39, N = 3.23, S = 7.39%.

The yield could not be improved by repeating the reaction under an atmosphere of nitrogen. The yield was only 2% when the reaction was done at 0°.

Thin-layer chromatography of the mother liquor did not show other isolable products.

E. The addition of thiazole to dimethyl acetylenedicarboxylate in diethyl ether.

a) Thiazole (8.50 gm., 100 mmole) was dissolved in diethyl ether (100 ml.) and dimethyl acetylenedicarboxylate (28.4 gm., 200 mmole) was added slowly with stirring at room temperature. The reaction was allowed to proceed with occasional stirring at room temperature for 96 hrs. At the end of this time, the solvent was removed and traces of starting material were removed under water pump vacuum (13 mm). The residue was dissolved in the minimum amount of methylene chloride and 5 (200 ml) fractions were taken. After removal of solvent, trituration with methanol and recrystallisation from a mixture

of methylene chloride and methanol (1:1), tetramethyl 8aH-azeto[1,2-d][1,4]thiazepine-1,7,8,8a-tetracarboxylate (66) (2.33 gm., 6.3%), was obtained as orange prisms, m.pt. 148-150.0°. Further elution with methylene chloride containing 10% ether was conducted and 7 (500 ml.) fractions were collected. After removal of solvent, trituration with methanol and recrystallisation in the usual manner, (a) tetramethyl-5H-thiazolo[3,2-a]pyridine-5,6,7,8-tetracarboxylate (99), (300 mg. 0.8%) was obtained as yellow needles, m.pt. 143.0 - 147.0°.

Found C = 49.10, H = 3.80, N = 4.07, S = 9.09

$C_{15}H_{15}NO_8S$ requires C = 48.82, H = 4.06, N = 3.79, S = 8.67%

Final elution with ether (2 litre) evaporation of solvent, trituration with methanol and recrystallisation in the usual manner gave (b) pentamethyl thiazolo[3,2-a]azepine - 5,6,7,8,9-pentacarboxylate (101), (220 mg., 0.5%) as light yellow prisms, fluorescent in solution, m.pt. 257.5 - 262.5°.

Found C = 48.77, H = 4.12, N = 3.36, S = 6.78

$C_{18}H_{17}NO_{10}S$ requires C = 49.24, H = 3.87, N = 3.19, S = 7.13%

II. The addition of thiazoles to methyl propiolate

A. Preparation of propiolic acid and its methyl ester

a) The monopotassium salt of acetylenedicarboxylic acid (220 gm., 1.44 mole) and water (600 ml.) were heated on a boiling water bath for one hour until all the salt was

dissolved. After being boiled under reflux for two hours, and cooling, the solution was acidified with conc. HCl and saturated with ammonium sulphate (solid was present). The solution was extracted twenty times with 100 ml. portions of ether. After every five extractions, the acidity of the solution was checked and maintained at approximately pH 2 by the further addition of conc. HCl. The ether extracts were dried (sodium sulphate), filtered and evaporated. Any crystalline solid was filtered and washed with a small amount of ether. Final traces of ether were removed and the residue was cooled in an ice bath. A further amount of solid precipitated and was filtered and washed with dry ether as before. The ether washings were combined with the residue, evaporated and the residue distilled under reduced pressure giving propiolic acid (50 gm., 56%), B.pt. 63-70°/13 mm., (lit.[60] 83°/50mm).

b) Freshly distilled propiolic acid (48 gm., 1.2 mole) was added to a mixture of methanol (192 gm., 240 ml.) and conc. sulphuric acid (80 gm., 40 ml.), and the solution was left for two days with occasional stirring. At the end of this time, it was poured into water (500 ml.) and the resulting mixture was extracted five times with 100 ml. portions of ether. The ether extracts were combined and washed with water (30 ml.), sodium bicarbonate solution (50 ml.), and water (30 ml.), respectively, and dried (anhydrous sodium sulphate). [All of the above washings were combined with

the original solution that was extracted, acidified with mineral acid and saturated with ammonium sulphate as in the preparation of propiolic acid. Non-esterified acid was reclaimed by repeating, again, the exhaustive extraction procedure]. After removal of ether through a long Vigreux column, the ester was distilled at atmospheric pressure giving methyl propiolate (34 gm., 60%), B.pt. 102.0 - 103.0°. (lit.[81] 102°/742 mm).

B. The addition of thiazole to methyl propiolate in acetonitrile

a) Thiazole (1.60 gm., 20 mmole) was dissolved in acetonitrile (25 ml.) and methyl propiolate (3.36 gm., 40 mmole) was added with stirring. The reaction mixture was allowed to stand at room temperature for 96 hrs. The adduct was then filtered off and the mother liquor was evaporated under vacuum (13 mm.). The residue was dissolved in the minimum amount of dry methylene chloride and chromatographed on a column (28 cm. x 3.5 cm.) of alumina. Elution was with dry methylene chloride (1 litre). On evaporation of the solvent a small amount of a red oil was obtained which on trituration with a small amount of methanol gave a further crop of the adduct. Difficulty was experienced in recrystallising the combined adducts (81 mg.) from acetonitrile, due to decomposition as evidenced by decolorisation (a similar behaviour was observed when a solution of the adduct, in methanol or ethanol, was left at room temperature for 24 hr.) Recrystallisation from dry

methylene chloride gave 4,5,10,11-tetrahydro-6,12-dicarbomethoxy dithiazolo[1,2-a,1',2'-e][1,5]diazocine (105), (72 mg. 1.1%) as orange red needles, m.pt. 164.0 - 167.0°

Found C = 50.01, H = 4.28, N = 8.55

$C_{14}H_{14}N_2O_4S_2$ requires C = 49.70, H = 4.17, N = 8.28%.

The yield of product was increased to 760 mg. (2.2%) when the reaction was repeated on a 100 mmoles scale using only half the amount of solvent. [mol.wt. (mass spectrum) 338]

C. The addition of 2,4-dimethylthiazole to methyl propiolate in (a) acetonitrile and (b) methanol.

a) 2,4-Dimethylthiazole (2.26 gm., 20 mmole) was dissolved in acetonitrile (12 ml.) and methyl propiolate (3.36 gm., 40 mmole) was added with stirring. The reaction mixture was allowed to stand at room temperature for 10 days with occasional stirring and then volatile materials were removed under vacuum (13 mm.). Thin-layer chromatography showed that two products were present. The residue was dissolved in a minimum quantity of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. The column was eluted with a mixture of methylene chloride (500 ml.) and ether (500 ml.) and 10,100 ml., fractions were collected. After evaporation of solvent appropriate fractions were "seeded" with material obtained from a 1 mmole reaction. After trituration with methanol the

crystalline product was filtered, washed with a little methanol and dried in vacuo. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave orange yellow needles (60 mg.) corresponding to the most polar product observed by thin-layer chromatography. Other fractions did not yield any crystalline product and obtention of the least polar material was not realized.

b) The preceding reaction was repeated on the 5 mmole scale, in methanol which was shown to give only the most polar product by thin-layer chromatography. After 5 days the reaction mixture was "seeded" with the product from (1) above, and the mixture was allowed to stand at room temperature for a further 5 days. At the end of this time the crystalline product was filtered, washed with a little methanol and dried in vacuo. Solvent was evaporated from the mother liquors and traces were removed under vacuum (13 mm.). The residue was dissolved in a minimum amount of methylene chloride and brought onto a column (15 cm. x 3.5 cm.) of alumina. The column was eluted with methanol (1 litre) until no more yellow material was removed. On evaporation of solvent, seeding , and trituration with methanol a further yield of product was obtained, giving a total of 100 mg. of crude product. Four similar reactions, on the 5 mmole scale gave dimethyl 7,8-dihydro-3-methyl-9-

-(β-carbomethoxyvinyl)thiazolo[3,2-a]azepine-6,8-dicarboxylate (112), (390 mg., 5.4%), as yellow needles after recrystallisation from a mixture of methylene chloride and methanol (1:1), m.pt. 175.5 - 178.5°., mol.wt.[82] (mass spectrum) 365 .

Found C = 56.20, H = 5.24

$C_{17}H_{13}NO_6S$ requires C = 55.91, H = 5.20%.

D. The addition of 2-methylthiazole to methyl propiolate in acetonitrile .

a) 2-Methylthiazole (1.98 gm., 20 mmole) was dissolved in acetonitrile (12 ml.) and methyl propiolate (3.36 gm., 40 mmole) was added with stirring. The reaction mixture was allowed to stand at room temperature for 96 hrs. and then volatile materials were removed under vacuum (13 mm.). Two modes of work-up were employed (1) extraction with 1 and 2 $\bar{N}$ HCl and (2) chromatography in the usual manner.

1) The residue was dissolved in benzene (15 ml.) and each of two aliquots (5 ml.) was thrice extracted with 20 ml. portions of $1\bar{N}$ and $2\bar{N}$ HCl, respectively. The extracts were washed with ether (20 ml.), neutralised with washed calcium carbonate (product was found to be unstable to sodium bicarbonate washing) and thrice extracted with 50 ml. portions of ether. The extracts were combined and dried (potassium carbonate) and the solvent was evaporated. The small residue after trituration with methanol, gave orange

prisms (4 mg. from 1$\bar{N}$ HCl; 2 mg. from 2$\bar{N}$ HCl), m.pt. 145.0 - 148.0°.

2) The final aliquot (5 ml.) was chromatographed on a column (10 mm. x 1.8 cm.) of alumina and eluted with a mixture of methylene chloride (350 ml.) and ether (250 ml.) Homogeneous fractions were combined, solvents evaporated, and the appropriate fractions "seeded" with authentic material. After being triturated with a small amount of methanol the crystalline product, after filtration and washing with a small amount of methanol gave orange prisms (10 mg.), m.pt. 146.0 - 148.0°. There was not enough material for characterisation.

III. Studies of the reactions of the adducts

A. Studies of the [3,4,0]-bicyclic structures 8aH-thiazolo [3,2-a] pyridines.

a) Attempted thermal isomerisation of compounds (61) and (63).

Samples of the compounds (61) and (63) (100 mg.) were separately sublimed using the heating block (120°/0.1 mm.). Both samples, after sublimation, were found to be identical to starting material by mixed melting point and thin-layer chromatography.

b) The reaction of compound (61) with mercuric acetate

A mixture of the compound (61), (25 mg.), benzene

(25 ml.), mercuric acetate (10 mg.) and glacial acetic acid (0.5 ml.) was gently warmed on the steam bath for 15 minutes. The reaction mixture was poured into water (50 ml.) and the water extracts were separated, extracted thrice with methylene chloride (50 ml.), dried (anhydrous sodium sulphate) and evaporated. The residue could not be crystallised and thin-layer chromatography showed a number of components. The reaction was not further investigated.

c) Reaction of compound (61) with cyanogen bromide

A solution of the compound (61), (50 mg.) in dry methylene chloride (10 ml.) was added dropwise to a solution of cyanogen bromide [70] (25 mg.) in dry methylene chloride (20 ml.), at room temperature. At the end of two hours the yellow solution was poured into water (50 ml.), neutralised with sodium bicarbonate, and extracted thrice with 50 ml. portions of methylene chloride. The extracts were dried (anhydrous sodium sulphate) and evaporated. The residue which could not be crystallised, showed a complex mixture of yellow products by thin-layer chromatography. The reaction was not further investigated.

d) Attempted hydrolysis of the 8a*H*-thiazolo[3,2-*a*] pyridines.

The 8a*H*-thiazolo[3,2-*a*]pyridines could not be hydrolyzed due to their sensitivity to acids and bases,

(evidenced by their decolorisation and formation of sulphurous products in acid solution).

o) Raney nickel desulfurisation of compound (61)

1) A mixture of the compound (61), (100 mg.) and active (W-6) Raney nickel [71] (1 gm.) in absolute ethanol (1.5 ml.) was stirred at room temperature for 15 minutes. The Raney nickel was removed by filtration through a bed of celite. Thin-layer chromatography of the reaction mixture showed a mixture of polar products close to the origin. The reaction was not further investigated.

2) An acetone suspension of (W-6) Raney nickel [72,73] (10 gm.) was boiled under reflux for 30 minutes and then added to a solution of the compound (61), (397 mg., 1 mmole) in absolute ethanol (25 ml.). The mixture was stirred at room temperature for 15 minutes. The Raney nickel was removed by filtration through a bed of celite, solvent was evaporated, and the residue was triturated with dry methanol. No material crystallised and the residue was dissolved in a minimum amount of methylene chloride and brought onto a column (10 cm. x 1.8 cm.) of alumina. Elution with a mixture (1:1) of methylene chloride and ether (500 ml.) was attempted and 10,50 ml. fractions were collected. The fractions were checked for homogeneity by thin-layer chromatography and no separation of the polar products was

observed. The fractions were combined, solvent was evaporated, and rechromatography using 100% ether as eluent was attempted. Elution of the products was very slow but separation was still not achieved. The reaction was not further investigated.

f) Oxidation of the compound (61) with peracetic acid

The compound (61), (40 mg., 0.1 mmole) was dissolved in glacial acetic acid (15 ml.). The solution was heated to 80° and 30% hydrogen peroxide (3 ml.), 300 equiv.) was added with constant stirring. The reaction was allowed to proceed until the color changed to lemon yellow (0.5 min). The mixture was immediately poured into water (100 ml.), neutralized with sodium bicarbonate and thrice extracted with 50 ml. portions of methylene chloride. The combined extracts were washed with water (50 ml.) and dried over anhydrous sodium carbonate. After evaporation of solvent, the residue was triturated with methanol and the crystalline product was filtered, washed with methanol and dried in vacuo. The mother liquor was dissolved in a minimum amount of methylene chloride and chromatographed on a column (10 cm. x 1.8 cm.) of Woelm neutral alumina. Elution was with methanol and 5,50 ml. fractions were collected. Homogeneous fractions were combined and triturated with dry methanol, giving a further quantity of product, (combined

yield 5 mg.). The reaction was repeated on a 1 mmole scale giving yellow prisms (45 mg.). Thin-layer chromatography showed only one component but white crystals, observed during the determination of the melting point, could not be removed by recrystallisation. Similar reactions were performed using 1 equivalent, 20 equivalents and 100 equivalents of 30% hydrogen peroxide, and gave similar results .

g) Oxidation of compound (61) with pertifluoroacetic acid.

Pertrifluoroacetic acid [78] was prepared, according to the method used by Hart and Buehler, at a concentration of 42.3 mg./ml.

One equivalent of pertrifluoroacetic acid (0.4 ml.) was added dropwise to a stirred solution of the compound (61), (39.7 mg., 0.1 mmole) and dry methylene chloride (4 ml.) at room temperature. The reaction mixture was allowed to stand at room temperature for 15 min. and then washed successively with water (50 ml.), saturated sodium bicarbonate solution (50 ml.) and water (50 ml.). Work-up was the same as in f). The red oil obtained did not crystallise on trituration with methanol. Thin-layer chromatography showed at least 5 major products.

The reaction was repeated at 0° with similar results.

The reaction was repeated at 0° using 2 equivalents of pertrifluoracetic acid (0.8 ml.). The reaction was

allowed to stand for 5 min. and then "worked-up" in the usual manner. A crystalline product was isolated, filtered, washed with a little methanol and dried in vacuo. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave yellow prisms (10 mg.), m.pt. 174.0 - 176.0°.

Found C = 46.71; H = 4.33

$C_{17}H_{19}NO_{10}S$ requires C = 47.54, H = 4.43 %

(for a monoxide)

h) Oxidative-cleavage of the compound (61) with chromic acid

A cold saturated solution of chromium trioxide in glacial acetic acid (25 ml.) was added dropwise to a stirred solution of the compound (61), (2.0 gm., 5 mmole) in glacial acetic acid (100 ml.) at room temperature. Addition was stopped after the solution became permanently green. The solution was immediately poured into water (100 ml.), neutralised with sodium bicarbonate and extracted thrice with 100 ml. portions of methylene chloride. The extracts were dried (anhydrous potassium carbonate) and evaporated. The residue was triturated with dry methanol, and the resulting solid was filtered. It was extremely soluble in small quantities of most of the common solvents and could not be recrystallised. The product distilled as a colorless oil using the heating block (100 — 115° /0.1 mm.). On cooling, the oil crystallised to a waxy solid (1.0 gm., 61%), m.pt. 58.0 - 63.0° (redistillation gave m.pt.

62.0 - 64.0°). The purity of the distillate was determined on a Perkin Elmer 451 gas liquid chromatograph fitted with a 3% neopentyl glycol succinate on celite column (100-120 mesh), acid washed and silanized; temperature 235°. flow rate 80 ml./min. The distillate contained less than 0.5% impurity. Lassaigne's test was positive for nitrogen and negative for sulphur.

Found C = 51.46, H = 4.93, N = 4.09

$C_{14}H_{15}NO_8$ requires C = 51.71, H = 4.61, N = 4.31%

for tetramethyl 2-methylpyridine-3,4,5,6-tetracarboxylate (82)

1) Hydrolysis and decarboxylation of tetramethyl 2-methylpyridine-3,4,5,6-tetracarboxylate (82) to α-picoline.

The 2-methylpyridine tetraester (82), (500 mg.) was boiled under reflux with potassium hydroxide (excess) in methanol (25 ml.) for 0.5 hrs. At the end of this time the solution was acidfied with conc. hydrochloric acid, the precipitated acid filtered through a sintered glass funnel and dried in vacuo (300 mg., 72%).

The above tetraacid (300 mg.) was intimately mixed with an excess of soda-lime and placed in a tube fitted with a bulb. The mixture was slowly heated to 250° in a Wood's metal bath for 0.5 hr. At the end of this time the condensate was made alkaline with potassium hydroxide and extracted with ether (25 ml.). The extracts were dried

(potassium carbonate) and evaporated. The infra-red spectrum (smear) was coincident with the infra-red spectrum of an authentic sample of α-picoline.

i) The reaction of the compound (61) with dimethyl acetylenedicarboxylate in alcohols.

A solution of the compound (61), (100 mg., 0.25 mmole) in dimethyl acetylenedicarboxylate (200 mg., 1.4 mmole) and 5 ml. of a) ether, b) DMF, c) methanol and d) acetonitrile was left at room temperature for 96 hrs., with occasional shaking. At the end of this time, a white crystalline product had separated from the reaction in methanol. Reactions in a), b), and d) showed mainly starting material (thin-layer chromatography). When the reactions were performed in 0.5 $\bar{N}$ and 2.0 $\bar{N}$ mixtures of methanol and HCl (5 ml.), only a complex mixture of colorless, less polar materials were observed by thin-layer chromatography. Adducts from thiazole, 4-methyl-thiazole and trimethylthiazole did not form adducts even when boiled under reflux for 8 hours. The adduct from 2-ethyl-4-methylthiazole, under similar conditions, showed the presence of yellow material (thin-layer chromatography), but isolation was not attempted.

1) The reaction of the compound (61) in methanol.

A mixture of the adduct from 2,4-dimethyl-thiazole (1 gm., 2.5 mmole), dimethyl acetylenedicarboxylate (2.13 gm., 15 mmole) and dry methanol (100 ml.) was boiled

under reflux for 15 mins. and then left standing at room temperature for 4 days. The crystalline material was filtered, washed with a little methanol and dried in vacuo. Recrystallisation from methylene chloride and methanol (1:1) gave light yellow prisms (600 mg., 42%), m.pt. 132.0 - 135.0°.

Found C = 50.14, H = 5.12, S = 5.83

$C_{24}H_{29}O_{13}NS$ requires C = 50.45; H = 5.08, S = 5.60%

(a 1:1:1 adduct)

Ehrlich's test was negative. Lassaigne's test was positive for both nitrogen and sulphur.

2) The reaction of the compound (61) in ethanol

The above reaction was repeated on the 1.3 mmoles scale in ethanol. Recrystallisation of the adduct from methylene chloride and methanol (1:1) gave light yellow prisms (242 mg., 32%), m.pt. 156.5 - 157.0°.

Found C = 51.01, H = 5.21

$C_{25}H_{31}NO_{13}S$ requires C = 51.30, H = 5.30%.

(a 1:1:1 adduct)

Ehrlich's test was negative. Lassaigne's test was positive for both nitrogen and sulphur.

B. Studies of the [5,2,0]-bicyclic structures, 8aH azeto [1,2-d][1,4]thiazepines. (i.e. 1,4-thiazonines).

a) Attempted thermal isomerisation of compounds (71) and (74)

Samples of the compounds (71) and (74), (100 mg.) were sublimed separately using the heating block (180.0°/0.1 mm.).

Both samples of sublimate were found to be identical to authentic material by mixed melting point.

b) The reaction of compound (71) with mercuric acetate

A mixture of the compound (71), (25 mg.) benzene (25 ml.) mercuric acetate (10 mg.) and glacial acetic acid (0.5 ml.) was warmed gently on the steam bath for 15 min. "work-up" (as in III, A,b) gave mainly starting material and some material at origin, by thin-layer chromatography.

c) Attempted reaction of compound (71) with cyanogen bromide

A solution of the compound (71), (50 mg.) in dry methylene chloride (10 ml.) was added dropwise to a solution of cyanogen bromide [70] (25 mg.) in dry methylene chloride (20 ml.) at room temperature. "Work-up" (as in III, A,c) gave only starting material.

d) Attempted hydrolysis and decarboxylation of compound (71)

The compound (71), (383 mg., 1 mmole) was dissolved in dry methanol (25 ml.) and potassium hydroxide (excess) was added. The solution was boiled under reflux for 0.5 hr. and the potassium salt was filtered and dried in vacuo (450 mg., 93%). The tetrapotassium salt (450 mg.) was dissolved in a mixture of water (25 ml.) and conc. HCl (12 ml.), evaporated to 1/3 volume and the tetraacid precipitated. This acid decomposed, slowly, to a black insoluble solid on warming with a mixture (50 ml.) of water and conc. HCl (1:1). Attempted sublimation caused decomposition to the same black solid.

The tetrapotassium salt (100 mg.) was dissolved in a mixture (15 ml.) of water and conc. HCl (1:1) and allowed to stand overnight at room temperature. A dark red solid (60 mg.) precipitated and was filtered and dried in vacuo. The product was very soluble in hydroxylic solvents and could not be recrystallised.

e) Raney nickel desulfurisation of compound (71)

1) An acetone suspension of (W-6) Raney nickel[72,73] (10 gm.) was boiled under reflux for 30 minutes and then added to a solution of the compound (71), (38.3 mg., 1 mmole) in absolute ethanol (25 ml.). The mixture was stirred at room temperature for 15 minutes. The Raney nickel was removed by filtration through a bed of celite, solvent was evaporated, and the residue was triturated with dry methanol. The crystalline material obtained was found to be homogeneous by thin-layer chromatography. Recrystallisation from a mixture of methylene chloride and methanol (1:1), filtration and drying in vacuo gave a product (250 mg.), m.pt. 128.0 - 130.0°, believed to be the dihydropyridine (77).

Found C = 51.84, H = 4.89, S = 1.68

$C_{16}H_{19}NO_3$ requires C = 54.45, H = 5.38%.

2) A mixture of the compound (71), (383 mg., 1 mmole) and active (W-6) Raney nickel [71] (10 gm.) in absolute ethanol (15 ml.) was stirred at room temperature for 15 minutes. The

Raney nickel was removed by filtration thrcugh a bed of celite. Thin-layer chromatography of the reaction mixture showed the presence of a mixture of a yellow and a white material. The solvent was evaporated and chromatography of the residue as in (III,A,e) failed to separate the mixture. Rechromatography using 100% ether as the eluent was also unsuccessful.

3) Attempted desulfurisation of compound (71) by boiling under reflux in absolute ethanol for 2 hr. and "work-up" as in (III,A,e) gave similar results as in 2).

f) Oxidation of compound (71) with peracetic acid

A solution of the compound (71), (38.3 mg., 0.1 mmole) in glacial acetic acid (15 ml.) was heated to 80° and 30% hydrogen peroxide (3 ml., 300 equiv.) was added under constant stirring. The reaction was allowed to proceed until the color changed to lemon yellow (0.5 min.). The mixture was immediately poured into water (100 ml.). "Work-up" (as in III,A,f) gave a crystalline product, homogeneous by thin-layer chromatography, which was filtered, washed with a little methanol and dried in vacuo. The material was light-sensitive and after recrystallisation from a mixture of methylene chloride and hexane (1:1) under "red light" gave yellow prisms of tetramethyl 5-methyl-8aH-azeto[1,2-d][1,4]thiazepine sulfoxide-1,7,8,8a-tetracarboxylate (81), (36 mg.,91%),

m.pt. 181.5 - 183.0°.

Found C = 47.86, H = 4.28, N = 3.41, S = 8.09

$C_{16}H_{17}NO_9S$ requires C = 48.14, H = 4.23, N = 3.51, S = 8.04%.

A 1 mmole run gave lemon yellow prisms of the sulphoxide (81), (350 mg., 88%), m.pt. 181.0 - 183.0°.

Similar reactions were performed using the following concentrations of 30% hydrogen peroxide:

1) One equivalent - "Work-up", as above, gave a colorless gum which could not be crystallised.

2) 20 equivalents - "Work-up" gave the gum and traces of a more polar yellow material (less polar than material isolated from 300 equivalents as shown by thin-layer chromatography).

3) 100 equivalents - "Work-up" gave mainly equal mixtures of the yellow material, above, and the material isolated from reaction with 300 equivalents.

g) Oxidation of compound (71) with pertrifluoroacetic acid

One equivalent of pertrifluoroacetic acid (0.4 ml.), prepared according to a method used by Hart abd Buehler,[78] was added dropwise to a stirred solution of the compound (71), (38.3 mg., 0.1 mmole) and dry methylene chloride (4 ml.) at room temperature. The reaction mixture after standing for 15 min. before "work-up" (III,A,f) gave yellow prisms (35.6 mg., 90%), m.pt. 181.5 - 183.5° (182.0 - 183.0° on admixture with product from III,B,f).

A similar reaction using 2 equivalents of pertrifluoro-

acetic acid (0.8 ml.) and the usual "work-up" procedure gave a mixture of products (25 mg.) similar in composition to those of (III,B,f,3) above. Chromatography failed to separate the mixture. An alternative route required reoxidation of the monoxide (81), (310 mg.), with 1 equivalent of pertrifluoroacetic acid (5.8 ml.) to give light yellow prisms of tetramethyl 5-methyl-8aH-azeto[1,2-d][1,4] thiazepine sulfone - 1,7,8,8a-tetracarboxylate (225 mg., 70%), which could be recrystallised, from a mixture of methylene chloride and hexane (1:1), m.pt. 228.0 - 230.0° dec.

Found C = 46.03, H = 4.23, S = 7.44

$C_{16}H_{17}NO_{10}S$ requires C = 46.31, H = 4.12, S = 7.71%.

Thin-layer chromatography confirmed the product to be analogous to the less polar product from (III,B,f,3), above.

1) Isolation , hydrolysis and decarboxylation of tetramethyl pyridine-2,3,4,5-tetracarboxylate (78)

The above reaction, with 1 equivalent of pertrifluoroacetic acid, was repeated on the (4.0 gm., 10.5 mmole) scale. After "work-up" in the usual manner and reoxidation with 1 equivalent of pertrifluoroacetic acid, only (300 mg., 7%) of the product, m.pt. 228.0 - 230.0°, was obtained. The mother liquor gave a product on evaporation of solvent which, after filtration and recrystallisation from an equal volume of methylene chloride

and methanol gave white plates of tetramethyl-pyridine-2,3,4,5-tetracarboxylate (78), (800 mg., 24.3%), m.pt. 98.0 - 100.0°.

Found C = 50.31, H = 4.27, N = 4.79

$C_{13}H_{13}NO_8$ requires C = 50.18, H = 4.18, N = 4.50%

The pyridine tetraester (78), (500 mg,) was hydrolysed and decarboxylated [using the same conditions employed for the similar treatment of 2-methylpyridine tetraester (82)] to pyridine . The infra-red spectrum (smear) was coincident with that of an authentic sample.

h) Attempted oxidative-cleavage of the compound (71), with chromic acid.

A cold saturated solution of chromium trioxide in glacial acetic acid (25 ml.) was added dropwise to a stirred solution of the compound (71), (1.1 gm., 3 mmole) in glacial acetic acid (100 ml.) at room temperature. Addition was stopped after the solution became permanently green. The solution was immediately poured into water (100 ml.) and "work-up" (as in III,A,h) gave yellow prisms (500 mg.) which were found to be inhomogeneous by thin-layer chromatography (elution with methanol).

Repeated chromatography on a column (10 cm. x 1.8 cm.) of Woelm neutral alumina and elution with mixtures of ether and methanol (3:1), gave yellow prisms (10 mg. of pure product from 500 mg. of the mixture), m.pt. 98.0 - 101.0°.

i) Desulfurisation of compounds (71) and (66) with zinc dust

The compound (71), (2.0 gm., 5.2 mmole) was dissolved in hot glacial acetic acid (30 ml.) and zinc dust * (2.0 gm.) was carefully added in small portions. The mixture was boiled under reflux for 2 hrs. and then poured into water (100 ml.). Conc. HCl (25 ml.) was added and the mixture extracted twice with 250 ml. portions of ether. The aqueous solution was neutralised with sodium bicarbonate and exhaustively extracted 10 times with 100 ml. portions of ether. The ether extracts were combined, washed with water (100 ml.), dried (anhydrous potassium carbonate) and evaporated. The residue crystallised on trituration with a small amount of methanol and was filtered, washed with a little methanol and dried in vacuo.

Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave lemon yellow prisms of the dihydropyridine (72), (250 mg.) m.pt. 171.0 - 179.0°.

Lassaigne's test was positive for nitrogen and negative for sulphur.

** Found C = 49.59, H = 5.18, N = 4.87, O = 40.32

$C_{13}H_{15}NO_8$ requires C = 49.85, H = 4.79, N = 4.48, O = 40.90%.

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* (B.D.H. Analar)

** By A. Bernhardt, Max-Planck-Institute, Mülheim, Germany

The compound (66), (2.0 gm., 5.5 mmole) was dissolved in hot glacial acetic acid (30 ml.) and zinc dust (2.0 gm.) was carefully added in small portions. The mixture was boiled under reflux for 2 hrs. and then poured into water (100 ml.). The "work-up" was the same as that employed above. The residue crystallised on trituration with methanol. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave lemon yellow prisms (200 mg.), m.pt. 171.0 - 173.0°. The thin-layer chromatogram, infra-red and proton magnetic resonance spectra were all coincident with the product (70).

C. Studies of the [3,5,0]-bicyclic structures, 5,6 dihydro thiazolo[3,2-a] azepines and the methyl propiolate adducts.

a) Attempted thermal isomerisation of compounds (87) and (88).

Samples of the compounds (87) and (88), (100 mg.) were sublimed separately using the heating block (180.0°/ 0.1 mm.). Both samples of the sublimate were found to be identical to authentic material by mixed melting point.

b) Attempted Desulfurisation of compound (88) with mercuric acetate.

The reaction of the compound (88), (25 mg.) with mercuric acetate (10 mg.) as in (III,A,b) gave a mixture of polar products by thin-layer chromatography.

c) Attempted hydrolysis and decarboxylation of 1) compound (88) and 2) compound (105)

1) Similar results were obtained when the hydrolysis of the compound (88), (433 mg., 1 mmole) and decarboxylation of the tetra acid was attempted as in (IV,B,d) above.

2) The diazocine (105), (100 mg.) was dissolved in methanol and warmed with potassium hydroxide (excess) until a precipitate was formed. After a short time the solution gradually became decolorized and a strong odor of ammonia was observed.

d) Attempted Raney nickel desulfurisation of 1) compound (89), 2) compound (105), 3) compound(111), and 4) compound (87)

1) An acetone suspension of Raney nickel (W-6)[72] (10 g.) was boiled under reflux for 30 minutes and then added to a solution of the compound (89), (433 mg., 1 mmole) in a mixture (50 ml.) of acetone and ethanol (1:1). The mixture was stirred at room temperature for 15 minutes. After removal of the Raney nickel by filtration through celite, thin-layer chromatography of the reaction mixture showed that only starting material was present.

When the reaction above, was repeated by boiling under reflux for 24 hour, starting material was obtained.

2) An acetone suspension of Raney nickel (W-6) was boiled under reflux for 30 minutes and then added to a solution of the diazocine (105), (338 mg., 1 mmole) in absolute ethanol (25 ml.). The mixture was stirred at room temperature for 15 minutes. The Raney nickel was removed by filtration through celite and thin-layer chromatography of the reaction mixture showed the presence of numerous polar products near the origin. The reaction was not further investigated.

3) An acetone suspension of Raney nickel (W-6)[72] was boiled under reflux for 30 minutes and then added to a solution of compound (111), (180 mg., 0.5 mmole) in absolute ethanol (20 ml.). The mixture was stirred at room temperature for 15 minutes. After removal of the Raney nickel by filtration through celite, thin-layer chromatography of the reaction mixture showed a mixture of polar products as in 2) above.

4) An ethanol suspension of Raney nickel (W-4),[79] (10 gm.) was added to a solution of the compound (87), (500 mg., 1.25 mmole) in ethanol and the mixture was boiled under reflux for 3 hrs. After filtration through celite, the solvent was removed under water pump vacuum. The solid obtained on trituration with methanol was recrystallised from methanol and gave, after drying in vacuo, tetramethyl 2,3-dihydro-1-ethyl-6-methylazepine-2,3,4,5-tetracarboxylate(91),

(310 mg., 67%), as lime green prisms, m.pt. 135.0 - 137.0°.

Found C = 55.07, H = 6.22, N = 3.97

$C_{17}H_{23}NO_8$ requires C = 55.31, H = 6.23, N = 3.79%.

e) Attempted oxidative-cleavage of 1) compound (87) and 2) compound (111) with chromic acid

1) A cold saturated solution of chromium trioxide in glacial acetic acid (25 ml.) was added dropwise to a stirred solution of the compound (87), (397 mg., 1 mmole) at room temperature. Addition was stopped after the solution became permanently green. The solution was immediately poured into water (100 ml.) and "work-up" as in (III,A,h) gave a mixture of products which could not be separated (as evidenced by the complexity of the thin-layer chromatogram). The reaction was not further investigated.

2) Oxidative-cleavage was attempted on the compound (111) using the above conditions. "Work-up" of the reaction mixture as in (III,A,h) also gave a mixture of products which could not be separated. The reaction was not further investigated.

IV. Preparation of Model Compounds

A. Preparation of cis and trans β-benzylthioacrylic acid and methyl ester.

These compounds were prepared according to the method of Owen and Sultanbawa.[98] The cis acid had melting point 144.0 - 145.0°; the trans acid had melting point 162.0 - 163.0°.

The cis acid (1.0 gm., 5.5 mmole) was dissolved in the minimum amount of dry ether and a solution of diazomethane in ether, was added until the solution was permanently yellow (10% excess). The solution was allowed to stand at room temperature for 0.5 hours and, after removal of ether, the residue was lightly triturated with dry methanol, filtered and dried in vacuo. Recrystallisation from a mixture of acetone and hexane (1:1) gave methyl cis-β-benzylthioacrylate (69), (950 mg., 91%), as white plates, m.pt. 49.5 - 50.5°.

Found C = 63.22, H = 5.98

$C_{11}H_{12}O_2S$ requires C = 63.46, H = 5.77%.

Similarly:

The trans acid (290 mg., 1.5 mmoles) gave methyl trans-β-benzylthioacrylate (70), (280 mg., 90%) as white needles, m.pt. 61.0 - 62.0°.

Found C = 63.58, H = 6.21.

$C_{11}H_{12}O_2S$ requires C = 63.46, H = 5.77%.

B. Preparation of dimethyl ethylthiomethylenemalonate (68)

This compound was prepared by the method of Gundermann,[99] substituting dimethyl malonate for diethyl malonate.

A mixture of ethyl orthothioformate[100] (10 gm.), dimethyl malonate (5.1 ml.), acetic anhydride (11 gm.) and anhydrous zinc chloride (800 mg.) was heated under reflux for 10 hours at 130.0 - 140.0° . At the end of this time the oil was decanted from the tarry residue (the remaining oil was transferred with a small amount of acetic anhydride) and distilled under water pump vacuum to remove the excess of acetic anhydride. The remaining oil was distilled under high vacuum and the fraction boiling at 120.0° /0.1 mm. was collected. Redistillation gave a light yellow, nearly colorless oil (2.53 gm., 27%) boiling at 115.0° /0.1 mm., which was found to contain traces of impurities by gas-liquid chromatography (G.L.C.). The major component was separated on the "autoprep" gas-liquid chromatograph using a 20' SE 30 column at a temperature of 250.0° and was analysed for dimethyl ethylthiomethylenemalonate (68), (1.8 gm., 19%).

Found C = 47.48, H = 5.30

$C_8H_{12}O_4S$ requires C = 47.06, H = 5.88%

C. Preparation of 2-methylthiophene-3,4-dicarboxylic acid and its dimethyl ester.

Diethyl 2-methylthiophene-3,4-dicarboxylate was prepared

according to the method of Kornfeld and Jones [101] and gave a white product, m.pt. 124.0 - 125°. .

The diethyl ester (4.77 gm.) was boiled under reflux for 1 hr. with a methanolic solution of potassium hydroxide (excess). The dicarboxylic acid was precipitated by addition of concentrated hydrochloric acid to the cooled mixture and gave small white needles (1.38 gm., 38%), m.pt. 203.0 - 207.0°, after recrystallisation from ethyl acetate. Analysis for sulfur was low and repeated recrystallisation raised the melting point to 208.0 - 210.0°.

dicarboxylic acid (m.pt. 203.0 - 207.0°) Found S = 14.40

dicarboxylic acid (m.pt. 208.0 - 210.0°) Found S = 7.20

$C_7H_6O_4S$ requires S = 17.22%.

The dicarboxylic acid (350 mg.), (m.pt. 203.0 - 207.0°), from the mother liquors, was methylated with diazomethane in the usual manner. After removal of ether, attempted crystallisation was unsuccessful but a solid product was obtained on cooling to -10°. The residue (400 mg.) was twice distilled using the heating block (90 — 95°. / 0.1 mm.). Two components, shown by G.L.C., were separated on an Autoprep A-700 "Automatic" preparative gas chromatograph, employing a 20' SE 30 column at a temperature of 250.0°.

The thiophene component (100 mg., 20%) gave a positive

Lassaigne's test for sulphur.

Found C = 49.89, H = 4.60

$C_9H_{10}O_4S$ requires C = 50.47, H = 4.68%.

for dimethyl 2-methylthiophene-3,4-dicarboxylate.

The other component (200 mg., 40%) gave a negative Lassaigne's test for sulphur and is believed to be the corresponding furan component.

V. Preparation of Pyrrolo[2,1-b] thiazoles

A. Decarboxylation studies of trimethylpyrrolo[2,1-b] thiazole-5,6,7-tricarboxylate (97)

(a) Preparation of the tripotassium salt (121) of pyrrolo[2,1-b] thiazole-5,6,7-tricarboxylic acid.

The trimethyl ester (97), (3.85 gm., 7 mmole), potassium hydroxide (excess) and methanol (50 ml.) were boiled under reflux for 0.5 hr. The precipitate (4.6 gm., 96%) consisting of the crude tripotassium salt (121) was filtered and dried in vacuo.

1) Thermal decarboxylation of the tripotassium salt (121) of pyrrolo[2,1-b] thiazole-5,6,7-tricarboxylic acid .

The tripotassium salt (121), (2.0 gm., 5.5. mmole) and calcium hydroxide (10.0 gm.) [83] were intimately mixed and divided into four equal portions. Each was placed in a combustion tube, fitted with a collecting bulb and cold finger, and heated to "red heat" with a

Meker burner. The condensates were collected, made alkaline with 50 ml. of dilute sodium hydroxide and steam distilled. The distillate (100 ml.) was extracted thrice with 25 ml. portions of ether, dried (potassium carbonate) and after being evaporated, a small amount of oil was left. The oil was dissolved in ethanol (3ml.) and a few drops of perchloric acid were added. The solid perchlorate, after filtration and drying in vacuo, gave pyrrolo[2,1-b] thiazolium perchlorate 5 mg.), as white granules, m.pt. 188.0 - 198.0° dec. (mixed m.pt. with authentic material 190.0 - 210.0° dec.)[4].

2) Attempted decarboxylation of the tripotassium salt of pyrrolo[2,1-b] thiazole-5,6,7-tricarboxylic acid using i) copper chromite and quinoline and (ii) copper chromite and triethanolamine.

Attempts to decarboxylate a mixture of the tripotassium salt (121), (1.0 gm., 2.8 mmole) with excess i) copper chromite/quinoline[84] and (ii) copper chromite/triethanolamine[85] at 180.0 - 200.0° under a moderate flow of nitrogen were unsuccessful (evidenced by a negative Ehrlich test).

b) Preparation of pyrrolo[2,1-b] thiazole-6-carboxylic acid and its methyl ester.

The tripotassium salt (121), (2.5 gm., 6.8 mmole) was heated for 1 hour on the boiling water bath with a mixture of concentrated hydrochloric acid (25 ml.) and water (75 ml.) until evolution of carbon dioxide had ceased.

At the end of this time the mixture was cooled and the precipitated acid was filtered. The mother liquor was evaporated to dryness using the rotary film evaporator. Both the precipitated solid and the residue were combined and sublimed using the heating block (90°/0.1 mm.). Resublimation gave pyrrolo[2,1-b]thiazole-6-carboxylic acid (500 mg., 45%), as white prisms, m.pt. 224.0 - 226.0°. It was characterised as the methyl ester (below).

The 6-carboxylic acid (122), (200 mg.), was dissolved in acetone (50 ml.) and a solution of diazomethane in ether was added dropwise with stirring until the yellow color persisted. The solvent was evaporated and the residue crystallised on cooling. Recrystallisation from methylene chloride and methanol (1:1), washing with a little methanol, filtering and drying in vacuo gave methyl pyrrolo[2,1-b]thiazole-6-carboxylate (123), (170 mg., 87%), as white plates, m.pt. 126.0 - 127.0°.

Found C = 53.18, H = 4.00

$C_8H_7NO_2S$ requires C = 53.04, H = 3.87%.

1) Attempted decarboxylation of pyrrolo[2,1-b]thiazole-6-carboxylic acid (122) using copper bronze.

The 6-mono acid (300 mg.) and copper bronze (4 gm.)[85] were intimately mixed and placed in a tube fitted with a bulb for collection of any distillate. The mixture was

heated at 300.0 - 325.0° (Wood's metal bath) for one-half hr. under water pump vacuum (13 mm.). At the end of this time, no volatiles were observed as a condensate in the bulb and only resublimed acid was present.

2) Attempted thermal decarboxylation of the ammonium salt of pyrrolo[2,1-b]thiazole-6-carboxylic acid.

The dry ammonium salt (124) * of the 6-carboxylic acid (2 gm.) was placed in a tube fitted with a bulb and slowly heated to 200°, under water pump vacuum (13 mm.).

There was no evidence of any condensate in the bulb after heating for 0.5 hour and a large quantity of resublimed ammonium salt (124) was recovered.

3) Attempted thermal decarboxylation of pyrrolo[2,1-b]thiazole-6-carboxylic acid with soda-lime.

The 6-carboxylic acid(122),(2 gm., 10 mmole) was intimately mixed with an excess of soda-lime and placed in a tube fitted with a bulb for collection of any distillate. The mixture was slowly heated to 200°, under water pump

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* Prepared by adding excess concentrated ammonium hydroxide to a solution of the acid in methanol, evaporation to dryness and further drying in vacuo.

vauuum (13 mm.), in a Wood's metal bath for one half hour. At the end of this time the condensate was made alkaline with sodium hydroxide and extracted with ether (50 ml.). The extracts were dried (potassium carbonate) and after evaporation of solvent only a trace of oil remained which gave a positive Ehrlich test. There was not enough product to convert to the perchlorate.

4) Preparation of 6-methylpyrrolo[2,1-b] thiazole from methyl pyrrolo[2,1-b] thiazole-6-carboxylate.

A solution of anhydrous aluminium chloride (2.4 gm., 18 mmole) in ether (10 ml.) was added dropwise to a rapidly stirred solution of lithium aluminium hydride (342 mg., 9 mmole) in ether (100 ml.). A solution of the 6-methyl ester (123), (500 mg., 3 mmole) in ether (50 ml.) was added dropwise at room temperature, to the mixed reagent over a period of one half hour. The mixture was allowed to stir for a further hour, then poured into water (100 ml.) and neutralised with solid sodium bicarbonate. The mixture was exhaustively extracted with ether (5, 100 ml. portions) dried(potassium carbonate) and the ether evaporated. The residue was distilled using the heating block (90 —— 100° /13 mm.) and the colorless distillate crystallised to colorless needles on cooling. Repeated distillation gave 6-methylpyrrolo[2,1-b] thiazole(125) (200 mg., 53%) as colorless needles, m.pt. 55.0 - 57.0°. (mixed m.pt. with authentic material, 56.0 - 58.0°).

i) Preparation of 6-methylpyrrolo[2,1-b] thiazolium perchlorate.

Excess perchloric acid (70 - 72%) was added to a solution of 6-methylpyrrolo[2,1-b] thiazole (500 mg., 3.7 mmole) in ethanol. The precipitated perchlorate was filtered and recrystallised from ethanol. Filtration, washing with a little ethanol and drying in vacuo gave 6-methylpyrrolo[2,1-b] thiazolium perchlorate (126), (810 mg., 81%), as white needles , m.pt. and mixed m.pt. 121.0 - 123.0° (lit.[4] 122.75 - 123.75°).

B. Cyclisation reactions of quaternary thiazolium salts in aprotic solvents .

a) Preparation of bromoacetone and phenacyl bromide.

Bromoacetone was prepared according to the method of Levine.[88]

Phenacyl bromide was prepared according to the method of Cowper and Davidson.[89]

b) Preparation of acetonyl and phenacylthiazolium salts.

The quaternary thiazolium salts were prepared according to the method of Molloy, Reid and (in part) Skelton.[12]

2,4-Dimethylthiazole and bromoacetone gave 3-acetonyl-2,4-dimethylthiazolium perchlorate, m. pt. 172.0 - 183,0°, on treatment of the bromide with excess perchloric acid.

2-Methylthiazole and bromoacetone gave 3-acetonyl-2-methylthiazolium perchlorate, m.pt. 124.0 - 126.0°.

2-Methylthiazole and phenacyl bromide gave 2-methyl-3-phenacylthiazolium bromide, m.pt. 204.0 - 205.0°.

c) General procedure

A solution of the quaternary thiazolium salt (5 mmole) in the solvent (15 ml.) was added to a solution or suspension of the base (5 mmoles, unless otherwise stated) in the same solvent (15 ml.) under nitrogen. The mixture was heated to the specified temperature, stirred for 5 hr. under nitrogen, cooled and poured into water. The residual oil was steam distilled, and the distillate was brought to pH5 before being extracted with ether. The extracts were washed free from acid, dried (anhydrous sodium sulfate) and evaporated. The residual oil in ethanol was treated with an excess of perchloric acid. Ether was added to complete the precipitation of the perchlorate. Details are given in Table 3.

Table 6. Cyclisation of 3-acetonyl 2,4-dimethylthiazolium perchlorate with bases in aprotic solvents.

Solvent	Base	Reaction Temp.	Yield(%)*
Dimethylformamide	Sodium acetate	110°	6
"	"	145°	8
"	Lithium acetate [a]	120°	6
"	Potassium cyanide [a]	120°	1
"	Triethylamine [b]	120°	1
Dimethyl Sulfoxide	Sodium acetate [c]	60°	2
"	Potassium t-butoxide [d]	60°	2

* Isolated as 3,6-dimethyl-5H-pyrrolo[2,1-b] thiazolium perchlorate, m.pt. 132.0 - 135.0°.

a) 10 mmole

b) 7 mmole

c) freshly fused

d) resublimed (185.0°/0.1 mm.)

Cyclisation of 2-methyl-3-phenacylthiazolium bromide in dry dimethylformamide , containing fused sodium acetate (2 equiv.) at 110° , gave an oil which crystallised on cooling. Vacuum distillation using a heating block (150 ——— 165° /0.1 mm.) and recrystallisation from absolute

ethanol gave 6-phenylpyrrolo[2,1-b]thiazole (52 mg. 5.2%) as yellow plates, m.pt. 187.0-192.0° (lit.[4], 200.0 - 202.0°.)

Cyclisation of 3-acetonyl-2-methylthiazolium perchlorate in dimethylformamide containing fused sodium acetate (2 equiv.) at 110° gave 6-methyl-5H-pyrrolo[2,1-b]thiazolium perchlorate (11 mg., 1%), as white plates, m.pt. 125.0 - 127.0°, after treatment of the residual oil with an excess of perchloric acid.

C. Attempted cyclisation of 3-acetonyl-2-methylthiazolium perchlorate with thionyl chloride.

A solution of thionyl chloride (10% excess) in dimethylformamide at 0° was added dropwise to a solution of 3-acetonyl-2-methylthiazolium perchlorate (100 mg., 0.39 mmole) in dimethylformamide at 0° and the mixture allowed to return, slowly, to room temperature. The mixture was heated at 100° for 10 minutes, the entire contents poured into water (50 ml.) and made alkaline with sodium hydroxide. After being extracted, twice, with 100 ml. portions of ether, the extracts were washed with water (60 ml.), dried (potassium carbonate) and evaporated. An Ehrlich test of the residue was negative.

D. Attempted preparation of pyrrolo[2,1-b]thiazole by cyclisation of 3-formylmethyl-2-methylthiazolium chloride.

A mixture of chloroacetal (20.0 gm., 130 mmole) and oxalic acid (12 gm.) was heated at 140° for 4 hr. and then distilled. The fraction boiling between 90.0 - 92.0° was

collected and gave chloroacetaldehyde hydrate (9.0 gm.,73%), (Lit, [103] b.pt. 90.0 - 91.0°.)

A mixture of 2-methylthiazole (2.0 gm., 20 mmole) and chloroacetaldehyde hydrate (1.8 gm., 20 mmole) was heated at 50° for 2 hrs. at 100° for 12 hrs. Acetic anhydride (50 ml.) was added to the dark viscous quaternary thiazolium salt and the mixture was boiled under reflux for 2 hrs with fused sodium acetate (3.3 gm., 2 equiv.). After cooling, the mixture was poured into water (500 ml.) and left at room temperature for 12 hrs. The solution was thrice extracted with 300 ml. portions of chloroform. The extracts were washed with water, dilute potassium carbonate solution and water, respectively, and dried (sodium sulphate). The residue, after evaporation of solvent, was boiled under reflux for 3 hr. with concentrated HCl (18 ml.) and water (60 ml.). The solution was made alkaline with potassium hydroxide and steam distilled. The distillate (1 litre) was acidified to pH5, extracted thrice with 100 ml. portions of ether and the ether extracts washed with water, potassium carbonate solution and water and dried (potassium carbonate) before evaporation. An Ehrlich test on the small residue was negative.

E. Attempted preparation of pyrrolo[2,1-b]thiazole-6-carboxylic acid.

A solution of ethyl bromopyruvate [91] (19.5 gm.,0.1M)

and 2-methylthiazole (9.9 gm., 0.1M) in chloroform (50 ml.) was boiled under reflux for 4 hr. Two-thirds of the solvent was evaporated and excess ether was added. After "oiling out" was complete, the ether layer was separated and traces of solvent and reactants were removed under water pump vacuum (13 mm.) leaving a partially crystalline residue of the quaternary thiazolium salt.

The quaternary thiazolium salt (9.0 gm., 32 mmole), dry acetic anhydride (90 ml.) and fused sodium acetate (5.3 gm., 2 equiv.) were boiled under reflux for 2 hr. The cooled mixture was poured into water (600 ml.) and allowed to stand at room temperature for 12 hrs. The mixture was extracted thrice with 100 ml. portions of chloroform and the chloroform extracts were washed with water, potassium carbonate solution and water and dried (sodium sulphate) before being evaporated. The semisolid residue was boiled under reflux for 2 hr. with a mixture of glacial acetic acid (15 ml.), HCl (5 ml.) and water (20 ml.). After this time, the mixture was poured into water (250 ml.) brought to pH5 by the addition of mineral acid and extracted thrice with 100 ml. portions of chloroform. The extracts were dried (potassium carbonate)and after evaporation of solvent, a light yellow crystalline residue (120 mg.) was obtained. Sublimation under high vacuum (0.1 mm.) at

130.0 - 135.0° gave a light yellow solid (110 mg.), m.pt. 180.0 - 190.0°. Methylation with diazomethane gave a mixture of esters. Thin-layer chromatography showed only a trace of material having the same polarity as an authentic sample of methyl pyrrolo[2,1-b] thiazole-6-carboxylate.

VI. Miscellaneous Reactions

A. The addition of 2-methylthiazoline to dimethyl acetylenedicarboxylate.

a) Preparation of 2-methylthiazoline

2-Methylthiazoline was prepared from N-acetyl-2-ethanolamine, according to the method of Wenker.[92] A sample was checked for purity on a Perkin Elmer 451 gas-liquid chromatograph utilising a one meter column containing 20% polyethylene glycol succinate at a temperature of 110°. The sample was found to be better than 99% pure product.

b) Preparation of the adducts from 2-methylthiazoline

2-Methylthiazoline (2.02 gm., 20 mmole) was dissolved in ether (25 ml.) and dimethyl acetylenedicarboxylate (5.68 gm., 40 mmole) was added with stirring at room temperature. The reaction was allowed to proceed with occasional stirring, at room temperature, for 96 hrs. At the end of this time the solid material was filtered and the reaction was allowed to continue until no more solid was formed. Thin-layer chromatography showed that the solid

consisted of a mixture of two adducts of similar polarity. The combined solids (crude yield 1.84 gm.) were dissolved in the minimum amount of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. The column was eluted with a mixture of methylene chloride (500 ml.) and ether (500 ml.) and 20,50 ml, fractions were collected.

The fractions were checked for homogeneity by thin-layer chromatography and combined where possible before being evaporated. The first 8 fractions gave a light yellow product after trituration of the residue with a small amount of methanol. Recrystallisation from a mixture of methylene chloride and methanol (1:1) gave light yellow prisms of (132) or (133), (555 mg.), m.pt. 94.8 - 97.3°.

Found C = 49.88, H = 5.12, N = 4.13 (S = 8.96)

$C_{16}H_{17}NO_8S$ requires C = 50.13, H = 4.62, N = 3.83 (S = 8.36)

Similarly, the latter fractions gave light yellow prisms of (134) or (135), (100 mg.), after trituration with methanol and recrystallisation from methylene chloride and methanol (1:1), m.pt. 159.5 - 161.5°.

Found C = 50.26, H = 5.02, N = 3.98 (S = 8.88)

$C_{16}H_{19}NO_8S$ requires C = 49.83, H = 4.93, N = 3.64 (S = 8.32)

The central fractions gave a mixture of the products (950 mg.). The mixture was rechromatographed in a similar manner.

B. The addition of benzothiazole to dimethyl acetylenedicarboxylate in a) methanol and b) acetonitrile.

a) Benzothiazole (2.70 gm., 20 mmoles) was dissolved in methanol (25 ml.) and dimethyl acetylenedicarboxylate (5.68 gm., 40 mmole) was added slowly with stirring at room temperature. The reaction was allowed to proceed with occasional stirring, at room temperature, for 96 hr. At the end of this time, the solvent was removed and any traces of starting material were removed under water pump vacuum (13 mm.). The residue was dissolved in the minimum amount of methylene chloride and brought onto a column (28 cm. x 3.5 cm.) of alumina. Thin-layer chromatography showed that the white and yellow adducts had widely different polarities and could be separated by chromatography. Elution with methylene chloride (1 litre), evaporation of solvent, trituration, and recrystallisation from methanol gave (a) yellow prisms **(137)**, **(510** mg.). m.pt. 231.0 - 233.0°. The product was relatively insoluble in non-polar solvents.

Found C = 50.65, H = 4.29, N = 3.42, S = 7.54

$C_{19}H_{17}NO_8S$ requires C = 54.50, H = 4.10, N = 3.41%.

(Compound III)[67]

Further elution with ether (1 litre), evaporation of solvent, trituration with methanol and recrystallisation from a mixture of methylene chloride and methanol (1:1), gave (b)

white prisms (136), (2.00 gm.), m.pt. 135.0 - 136.0°.

Found C = 52.61, H = 4.66, N = 3.94, S = 8.43%.

b) The reaction was repeated in acetonitrile. Work-up in the same manner gave (a) yellow prisms (137), (990 mg.) m.pt. 232.0 - 233.0° (mixed m.pt. with the product obtained in methanol was 231.0 - 233.0°) and (b) white prisms (136), (2.76 gm.), m.pt. 134.0 - 136.0° (mixed m.pt. with the product obtained in methanol was 134.0 - 136.0°).

C. Reaction of Phenacylthiazolium bromide with dimethyl acetylenedicarboxylate.

A mixture of thiazole (3 gm., 35 mmole), phenacyl bromide (7 gm., 35 mmole) and dry acetone (25 ml.) was boiled under reflux for 1 hr. At the end of this time the quaternary salt was filtered, washed well with ether and dried in vacuo. Recrystallisation from absolute ethanol gave 3-phenacylthiazolium bromide (6 gm., 60%), m.pt. 218.0 - 220.0°

Found N = 5.12

$C_{11}H_{10}BrNOS$ requires N = 4.93%.

A mixture of 3-phenacylthiazolium bromide (5.68 gm., 20 mmole), dimethyl acetylenedicarboxylate (2.84 gm., 20 mmole), triethylamine (2.20 gm., 10% excess)and dry methanol (35 ml.) was allowd to stand at room temperature for 96 hr. At the end of this time, solvent was removed (traces under water-

pump vacuum) and "work-up" was according to the procedure in (I,B,a,1). Trituration of the latter chromatographic fractions with ethyl acetate, gave a small amount of product. The combined product, after seeding of the other fractions, was recrystallised from a mixture of methylene chloride and methanol (1:1). The product, after filtration and drying in vacuo, gave yellow prisms (160 mg.), m.pt. 143.0° - 145.0°.

Found C = 63.18, H = 4.34, N = 3.03, (S = 6.01)

The above reaction was repeated on the same scale under the following conditions. A mixture of phenacylthiazolium bromide (5.68 gm., 20 mmole), dimethyl acetylenedicarboxylate (2.84 gm., 20 mmole) and dry methanol (35 ml.) was stirred under nitrogen for 15 minutes. At the end of this time, triethylamine (2.20 gm., 10% excess) was added dropwise under a constant flow of nitrogen, over a period of 15 minutes. The mixture was stirred under nitrogen for 45 hours. Thin-layer chromatography of the solid that separated showed it to be homogeneous. The product (1.1 gms.) was filtered, washed with a little methanol and dried in vacuo. Recrystallisation from a mixture of methylene chloride and methanol(1:1) gave yellow prisms (1.0 gm.), m.pt. 143.0 - 146.0° , unchanged on admixture with the product from the earlier run (above).

D. Attempted reactions of ditetrahydropyranyl acetylenedicarboxylate.

a) Preparation of ditetrahydropyranyl acetylenedicarboxylate.[96]

2,3 Dihydropyran (11.2 gm., 135 mmole) was added dropwise over one half hour to a suspension of acetylene dicarboxylic acid (7.6 gm., 67 mmole) and p-toluene-sulphonic acid monohydrate (8 mg.) in dry benzene (50 ml.) at 30 — 40°. The solution was neutralised with sodium bicarbonate, washed well with water (500 ml.) and dried (potassium carbonate). The benzene was carefully removed on rotary film evaporator at 50° leaving the crude ester (12.5 gm., 87%).

1) Attempted reaction of ditetrahydropyranyl acetylenedicarboxylate with 2-methylthiazole.

Reactions of the crude ester (530 mg., 2 mmole) and 2-methylthiazole (99 mg., 1 mmole) in 2 ml. of (a) ether, (b) DMF, (c) methanol, (d) acetonitrile, were left at room temperature for 96 hours, with occasional shaking. No reactions were observed to have taken place.

2) Attempted reaction of ditetrahydropyranyl acetylenedicarboxylate with phenacylpyridinium bromide

A mixture of the crude ester (1.4 gm., 2.5 mmole), phenacylpyridinium bromide [97] (1.4 gm.), triethylamine (1.5 ml) and acetonitrile (20 ml.) was stirred for 24 hr. at room temperature. After removal of solvent, thin-layer chromatography of the residue showed only starting materials. The reaction was not further investigated.

E. Attempted Reaction of Acetylene with 2-methylthiazole.

Dry N-methyl-2-pyrrolidone (25 ml.) was saturated with acetylene. 2-Methylthiazole (99 mg., 1 mmole) was added and the mixture allowed to stand under an ultra-violet lamp for 24 hrs. At the end of this time, thin-layer chromatography of the reaction mixture showed that no reaction had taken place.

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Table I. The ultraviolet absorption maxima (mμ) of 4H and 9aH-quinolizines in the solvents specified.

4H-quinolizines	Solvent	$\lambda_{max.}$ in mμ($10^{-4}\epsilon$)
18	methanol (M)	441(1.11),345(1.11),306(1.57),259(0.98),
	methanol + 8% $HClO_4$(P)	312(1.21).
21	M	439(0.97),360(1.3),311(1.0),262(0.74)
	P	317(0.07),273(0.91)
22	M	445(1.10),347(1.16),307(1.44),263(0.91)
	P	317(1.16),254(0.61)
27	M	442(1.29),360(1.82),310(1.26),267(0.97)
	P	323(0.12),271(1.07)
9aH-quinolizines		
20	M	441(0.46),289(1.48),235(1.48)
28	M	444(0.49),288(1.51),234(1.43)

Table II. The chemical shifts (δ) in the proton magnetic resonance spectra of 4H and 9aH-quinolizines in (a) deuterochloroform and (b) trifluoroacetic acids. (J values are in c/sec.)[42]

	3H	4H	6H	7H(Me)	8H	9H(Me)	9a-H(Me)	ester -
4H-quinolizines								
(18) a		6.06	7.70-7.40M	6.90T J(6,7;7,8)=14	7.70-7.40M	8.68 Q J(8,9;7,9)=11		3.93,3.8
b	5.26	6.46	9.11D J(6,7)=6	8.32T	8.86T J(7,8;8,9)=16	8.38D J(8,9)=8		4.20,4.1
(21) a		6.11	7.52Q J(6,7;6,8)=8	7.93T J(6,7;7,8)=14	7.67Q J(7,8;6,8)=8	2.28(Me)		3.94,3.7
b	5.72	6.89	8.91D J(6,7)=7	8.15T	8.66D J(7,8)=8	2.84(Me)		4.12,4.1
(22) a		6.02	7.38D J(6,8)=1	2.29(Me)	7.42Q J(8,9;6,8)=10	8.62D J(8,9)=9		3.93,3.8
b	5.20	6.33	8.87	2.71(Me)	8.60D J(8,9)=8	8.13D J(8,9)=8		3.95,3.8
(27) a		6.08	7.40	2.27(Me)	7.53	2.27(Me)		3.93,3.7
b	5.66	6.78	8.68	2.67(Me)	8.48	2.67(Me)		4.11,4.1

Table II contd.

	3H	4H	6H	7H(Me)	8H	9H(Me)	9a-H(Me)	ester -
9aH-quinolizines								
(20) a			6.22D J(6,7)=7	5.95-5.73M 2 protons		1.81(me)	4.00D J = 1	3.91,3.9
(28) a			6.07	1.81(Me)	5.78D J(8,9a)=2	1.81(Me)	5.08D J(8,9a)=2	3.89,3.8
(43) a			6.37D	5.57T J(6,7;7,8)=14	6.20Q J(7,8;8,9)=16	5.86D J(8,9)=9	1.82(Me)	3.98,3.8

D = doublet, T = triplet, Q = quadruplet, M = multiplet

Table 3. The chemical shifts (δ) in the proton magnetic resonance spectra of the (3,4,0), (5,2,0) and (3,5,0) - bicyclic structures in deuterochloroform (J values are in c./sec.). Structures are indicated by formulae numbers.

	2H	3H	4H	5H	6H	9H	$2CH_3$	$3CH_3$	$4CH_3$	$5CH_3$	$8aCH_3$	$9CH_3$	$2CH_2$	$8aCH_2$	
(3,4,0)															
(61)	5.70 J(2H-$3CH_3$) 1.1							2.02 J($3CH_3$-2H) 1.1			1.43				3.9
(63)	5.68 J(2H-$3CH_3$) 1.1							2.01 J($3CH_3$-2H) 1.1			0.91T			1.72Q	3.8
(64)							1.91	1.98			1.43				3.8
(5,2,0)															
(66)	8.13		6.02D 6.52D J(4H-5H) 4.6												3.92
(71)	8.07		5.73 J(4H-$5CH_3$) 1.3							2.12 J($5CH_3$-4H) 1.3					3.90
(72)			6.05D 6.74D J(4H-5H) 4.7				2.67								3.86
(73)				6.53 J(5H-$4CH_3$) 1.2			2.63		2.03 J($4CH_3$-5H) 1.2						3.92

Table 3 cont.

	2H	3H	4H	5H	6H	9H	$2CH_3$	$3CH_3$	$4CH_3$	$5CH_3$	$8aCH_3$	$9CH_3$	$2CH_2$	$8aCH_2$	ester - Me
(5,2,0)															
(74)			6.01D 6.33D J(4H-5H) 4.8				0.92T						1.75Q		3.93, 3.87, 3.80, 3.71
							$J(2CH_3-2CH_2)$ 7.2								
			6.06D 6.76D J(4H-5H) 4.9				1.32T						3.10Q		
							$J(2CH_3-2CH_2)$ 7.5								
(3,5,0)															
(85)	6.24D 6.60D J(2H-3H) 4.6			5.59D 5.36D J(5H-6H) 5.3		5.12									3.85, 3.80, 3.71, 3.62
(87)	6.29D 6.72D J(2H-3H) 4.5			5.66D 5.36D J(5H-6H) 5.3								1.82			3.85, 3.78, 3.72, 3.60
(88)	5.97 $J(2H-3CH_3)$ 1.3			5.70D 5.45D J(5H-6H) 5.4		5.10		2.49 $J(3CH_3-2H)$ 1.3							3.85, 3.80, 3.70, 3.62
(89)				6.04D 5.46D J(5H-6H) 5.3		5.20									3.85, 3.78, 3.69. 3.60

D = doublet, T = triplet, Q = quadruplet

Table 4. Ultraviolet absorption spectra

Compound	Solvent M = Methanol P = Methanol containing 2% (v/v) of 70% (w/w perchloric acid	λ max. in mμ (log ε)
(60)	M	345 (3.80)
(61)	M	215B (4.09), 239B (4.13), 295 (4.24), 446 (3.72)
(63)	M	211B (3.91), 235B (3.92), 298 (4.00), 454 (3.53)
(64)	M	208B (3.78), 233B (4.01), 298 (4.06), 447 (3.63)
(65)	M	342 (3.93)
(66)	M	225 (4.26), 282 (4.33), 430 (3.63)
(Compound I)[67]	M	227, 283, 435
(71)	M	227 (4.18), 285 (4.33), 441 (3.65)
(Compound II)[67]	M	228, 287, 445
(72)	M	224 (4.11), 283 (4.32), 428 (3.64)
(73)	M	230 (3.96), 284 (4.20), 436 (3.54)
(74)	M	225 (4.08), 285 (4.27), 428 (3.61)
(77)	M	259 (4.10), 268S (3.92), 392 (3.71)
(79)	M	255 (3.82), 262S (3.78), 391 (3.66)
(81)	M	258 (4.20), 312S (3.62), 398 (3.48)
(85)	M	220B (3.83), 440 (4.51)
	P	245B (3.61), 310 (4.23)
(87)	M	217B (3.94), 268 (2.10), 448 (4.49)
	P	230B (3.57), 296 (4.02)

Table 4, cont.

(88)	M	268B (4.33), 443(4.50)
	P	267B (3.72), 321 (3.85)
(Compound XIV)[67]	M	557
	P	246, 324, 335S
(89)	M	221 (4.09), 261 (3.63), 314 (3.27), 429 (4.49)
(Compound XI)[67]	M	269, 320S, 429
	P	254S, 259, 344
(91)	M	220B (3.66), 268 (2.10)
(92)=(Compound XV)[67]	M	247, 378
(99)	M	248 (3.88), 308 (4.24), 412 (4.12)
(100)=(Compound VI)[67]	M	262, 278S, 385
(101)=(Compound VIII)[67]	M	242, 317S, 326, 423
(105)	M	238 (3.90), 317 (3.77), 444S (3.07)
(111)	M	209 (3.80), 242 (3.72), 320S (1.20), 412 (4.20), 439 (4.26)
(132), (133)	M	211B (3.94), 273 (3.79), 428 (4.08)
(136)	M	227 (4.15), 254S (3.88)
(137)	M	216 (4.01), 270 (3.97), 294 (3.76), 424 (3.71)
(138) = (Compound III)[67]	M	223, 270, 295, 427.

Compounds included in brackets are considered to be analogues.

B = broad, S = shoulder

Table 5. Infra-red spectra in the 5-7 μ region

Compound	Solvent	υ_{max} in μ
(60)	chloroform	5.63, 5.76, 5.90S, 6.10, 6.23, 6.30, 6.52, 6.68, 6.91
(61)	"	5.74, 5.80, 5.84S, 5.90, 6.10S, 6.14, 6.32, 6.75, 6.87, 6.98
(63)	"	5.74, 5.80, 5.84S, 5.89, 6.12S, 6.14, 6.32, 6.75, 6.87, 6.98
(64)	"	5.76, 5.79, 5.84S, 5.90, 6.12S, 6.14, 6.33, 6.75, 6.87, 6.98
(65)	"	5.62, 5.78, 5.88S, 6.10, 6.20, 6.33, 6.52, 6.68, 6.92
(66)	"	5.75, 5.84S, 5.91S, 6.10, 6.24, 6.32, 6.44, 6.72, 6.87, 6.98
(Compound I)[67]	"	5.75, 5.80, 5.84S, 5.91S, 6.24, 6.68, 6.87, 6.98
(71)	"	5.80, 5.90S, 6.24, 6.68, 6.87, 6.98
(Compound II)[67]	"	5.74, 5.87S, 6.24, 6.63, 6.96
(72)	"	5.79, 5.83S, 5.90, 6.12, 6.15, 6.32, 6.75, 6.87, 6.98
(73)	"	5.80, 5.84S, 5.90, 6.12, 6.15, 6.32, 6.44, 6.72, 6.86, 6.98
(74)	"	5.80, 5.84, 5.90, 6.12, 6.14, 6.32, 6.76, 6.87, 6.98
(77)	"	5.68S, 5.92, 6.31, 6.35, 6.45, 6.58, 6.60, 6.82, 6.97
(78)	"	5.65, 5.72, 5.80, 5.92, 6.24, 6.41, 6.55, 6.58, 6.86, 6.96
(79)	nujol	5.70, 5.84, 5.88S, 5.91, 6.10S, 6.22, 6.58, 6.70, 6.85, 6.98
(81)	chloroform	5.76S, 5.82, 5.88, 6.015S, 6.32, 6.68, 6.84, 6.98
(82)	"	5.65, 5.70, 5.82, 5.91, 6.24, 6.40, 6.55, 6.58, 6.84, 6.98
(85)	"	5.65S, 5.75, 5.90, 6.20, 6.62, 6.98
(87)	"	5.67S, 5.77, 5.93, 6.15, 6.62, 6.97
(88)	"	5.68S, 5.75, 5.90, 6.14, 6.62, 6.97
(Compound XIV)[67]	"	5.68S, 5.77. 5.93, 6.16, 6.64, 6.95
(89)	"	5.76, 5.92, 6.18S, 6.27, 6.57, 6.84, 6.97
(Compound XI)[67]	"	5.76, 5.90, 6.22S, 6.27, 6.57, 6.84, 6.97

Table 5 cont.

	chloroform	
(91)	"	5.76, 5.84, 5.91, 6.11S, 6.22, 6.68, 6.86S, 6.95
(92) = (Compound XV)[67]	"	5.76, 5.85, 6.11, 6.41, 6.68, 6.88S, 6.95
(97)	"	5.77, 5.84, 6.18S, 6.20, 6.63, 6.82, 6.98
(99)	"	5.68S, 5.76S, 6.11, 6.20, 6.40, 6.52, 6.85S, 6.95
(100) = (Compound VI)[67]	"	5.72, 5.79, 5.87S, 5.92, 6.01S, 6.23, 6.60. 6.69, 6.72 6.87, 6.98
(101)	"	5.60, 5.72, 5.87, 5.98, 6.24, 6.32
(Compound VIII)[67]	"	5.63, 5.74, 5.83, 5.90, 5.98, 6.25, 6.41, 6.52, 6.66, 6.86 6.99
(105)	"	5.78S, 5.92, 6.25, 6.68, 6.87, 6.98
(111)	"	5.76, 5.82, 6.01, 6.42, 6.69S, 6.70, 6.88S, 6.97
(123)	"	5.78, 5.84S, 6.42, 6.58, 6.82, 6.98
(125)	"	6.28, 6.45, 6.50S, 6.84, 6.97
(132), (133)	"	5.66S, 6.01, 6.32S, 6.28, 6.60, 6.84, 6.98
(134), (135)	"	5.72S, 6.01, 6.20S, 6.28, 6.40, 6.58, 6.85, 6.98
(136)	"	5.65, 5.76, 5.82, 8.90S, 6.18, 6.32, 6.52, 6.75, 6.95
(137)	"	5.62S, 5.74, 5.82, 5.90S, 6.58, 6.75, 6.98
(138) = (Compound III)[67]	"	5.50(weak), 5.74, 5.86, 6.20, 6.59, 6.75, 6.95

S = shoulder

Compounds included in brackets are considered to be analogues.